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(54) Title: NUCLEIC ACIDS ENCODING ZINC METALLOPROTEASES

ADAM-TS RELATED PROTEIN-1 (ADAM-TSR1)



ADAM-TSR1 525 a.a. N- 1

SIGNAL PEPTIDE

METALLOPROTEASE

DISINTEGRIN-LIKE DOMAIN

THROMBOSPONDIN TYPE I REPEAT

CYSTEINE-RICH DOMAIN

CYSTEINE-POOR DOMAIN

UNIQUE DOMAINS

(57) Abstract: Isolated mammalian proteins having disintegrin-like and metalloprotease domains with thrombospondin type I motifs, i.e., ADAMTS proteins, are provided. The proteins are ADAMTS-5, ADAMTS-6, ADAMTS-7, ADAMTS-8, ADAMTS-9 and ADAMTS-10, collectively referred to as "ADAMTS-N". The present invention also provides isolated polynucleotides which encode an ADAMTS-N protein or a variant thereof, polynucleotide sequences complementary to such polynucleotides, vectors containing such polynucleotides, and host cells transformed or transfected with such vectors. The present invention also relates to antibodies which are immunospecific for one or more of the ADAMTS-N proteins. The present invention also relates to a protein referred to hereinafter as ADAMTS-R1 (ADAM-TS Related protein-1) and the polynucleotides which encode such protein.



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NUCLEIC ACIDS ENCODING ZINC METALLOPROTEASES

Background of the Invention

This invention relates to isolated nucleic acid -molecules

5 which encode proteins belonging to a zinc metalloprotease family.

The zinc metalloproteases have been implicated in a variety of diseases and development disorders that involve* enhanced or depressed proteolysis of components of the extracellular matrix, receptors, or other extracellular molecules.

- More particularly, the invention relates to isolated nucleic acid molecules encoding proteins belonging to a subfamily of zinc metalloproteases referred to as "ADAMTS", an abbreviation for A Disintegrin-like And Metalloprotease domain with ThromboSpondin type I motifs. Proteins in the ADAMTS subfamily all possess a Zn protease catalytic site consensus sequence (HEXXH+H), which suggests
 - an intact catalytic activity for each of these proteins. The ADAMTS proteins also have putative N-terminal signal peptides and lack transmembrane domains, which suggests that the proteins in this subfamily are secreted. The proteins in the ADAMTS subfamily also
- 20 possess at least one thrombospondin type (TSP1) motif, which suggests a binding of these proteins to components of the extracellular matrix (ECM) or to cell surface components.

Members of the ADAMTS subfamily of proteins are ADAMTS-1,
ADAMTS-2, ADAMTS-3, and ADAMTS-4. ADAMTS-1 protein is selectively
25 expressed in colon 26 adenocarcinoma cachexigenic sublines. ADAMTS-1
mRNA is induced by the inflammatory cytokine interleukin-1 in vitro
and by intravenous administration of lipopolysaccharide in vivo.
Thus, the ADAMTS-1 protein is believed to play a role in tumor
cachexia and inflammation.

The ADAMTS-2 protein is also known as procollagen I/H aminopropetide processing enzyme or PCINP. The ADAMTS-2 protein catalyzes

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cleavage of native triple-helical procollagen I and procollagen II.

The ADAMTS-2 protein also has an affinity for collagen XIV. Lack of the ADAMTS-2 protein is known to cause dermatosparaxis in cattle, or Ehlers-Danlos syndrome type VIIC (EDS-VIIC) in humans. EDS-VIIC is characterized clinically by severe skin fragility, and biochemically by the presence in skin of procollagen which is incompletely processed at the amino terminus. Thus, it is believed that the ADAMTS-2 protein plays a role in processing of procollagen to mature collagen, an essential step for correct assembly of collagen into 10 collagen fibrils. The ADAMTS-3 protein is similar in sequence to ADAMTS-2 and may have similar function.

The ADAMTS-4 protein catalyzes cleavage of the core protein of the extracellular matrix proteoglycan, aggrecan. Aggrecan degradation is an important factor in the erosion of articular cartilage in arthritic disease. Aggrecan fragments have been identified in cultures undergoing cartilage matrix degradation and in arthritic synovial fluids. Therefore, overexpression or activation 10 of ADAMTS-4 protein may be related to both inflammatory and non-inflammatory arthritis.

- On the basis of the structure, location, and the demonstrated proteolytic activity of ADAMTS proteins 1-4, it is expected that other members of the ADAMTS subfamily play a role in the cleavage of proteoglycan core proteins that are found in the extracellular matrix, such as, for example, versican, brevican, neuracan, NG-2,
- 25 aggrecan, as well as molecules such as collagen. It is also expected that other members of the ADAMTS subfamily play a role in embryogenesis, implantation of a fertilized egg, angiogenesis, arthritic degradation of cartilage, inflammation, nerve regeneration, tumor growth, and metastases.
- Thus, it is desirable to have other members of the ADAMTS

subfamily of proteins, the nucleic acids that encode such proteins, and antibodies that are specific for such proteins. Such molecules are useful research tools for studying development of the extracellular matrix during embryogenesis and fetal development, and 5 for studying disorders or diseases that are characterized by improper development of the extracellular matrix or enhanced or reduced destruction of the extracellular matrix. Such molecules, particularly the nucleic acids and the antibodies, are also useful tools for diagnosing such diseases or for monitoring the efficacy of therapeutic agents that have been developed to treat such diseases.

Summary of the Invention

The present invention provides novel, isolated, and substantially purified proteins having the characteristics of an 15 ADAMTS protein. The novel proteins are referred to hereinafter individually as "ADAMTS-5", "ADAMTS-6", "ADAMTS-7", "ADAMTS-8", "ADAMTS-9" and "ADAMTS-10", and collectively as "ADAMTS-N". In one embodiment, the ADAMTS-5 protein is a mature mouse protein which comprises amino acid 231 through amino acid 930 of the sequence set 20 forth set forth in SEQ ID NO: 2. In another embodiment, ADAMTS-5 is a human ADAMTS-5 protein which comprises amino acid 1 through amino acid 518 of the sequence set forth in SEQ ID NO: 4. In one embodiment, mature human ADAMTS-6 protein comprises amino acid 245 through amino acid 860 of SEQ ID NO: 6. In one embodiment, mature 25 human ADAMTS-7 protein comprises amino acid 233 through amino acid 997 of the sequence set forth in SEQ ID NO: 8. In one embodiment, mature ADAMTS-8 protein is a mouse protein which comprises amino acid 229 through amino acid 905 of the sequence set forth in SEQ ID NO: In another embodiment, ADAMTS-8 protein is a human protein which 30 comprises amino acid 1 through amino acid 245 of the sequence set forth in SEQ ID NO: 12. In one embodiment, mature ADAMTS-9 protein

is a human protein which comprises amino acid 236 through amino acid 1882 of the sequence set forth in SEQ ID NO: 14. In another embodiment, ADAMTS-9 protein is a mouse protein which comprises amino acid 1 through amino acid 974 of the sequence set forth in SEQ ID NO:

- 5 16. In one embodiment, mature ADAMTS 10 protein is a human protein which comprises amino acid 212 through amino acid 1081 of the sequence set forth in SEQ ID NO: 18. In another embodiment, ADAMTS-10 protein is a mouse protein which comprises amino acid 1 through amino acid 547 of the sequence set forth in SEQ ID NO: 20.
- The present invention also provides isolated polynucleotides which encode an ADAMTS-N protein or a variant thereof, polynucleotide sequences complementary to such polynucleotides, vectors containing such polynucleotides, and host cells transformed or transfected with such vectors. The present invention also relates to antibodies which are immunospecific for one or more of the ADAMTS-N proteins. The present invention also relates to a protein referred to hereinafter as ADAMTS-R1 (ADAM-T-S Related protein-1) and the polynucleotides which encode such protein. In one embodiment, the ADAMTS-R1 protein comprises amino acid 1 through amino acid 525 of the sequence set

Brief Description of the Drawings
Figure 1 shows an amino acid sequence (SEQ ID NO:2) of a full-length
mouse ADAMTS-5 protein and a nucleic acid sequence (SEQ ID NO: 1)
which encodes such protein.

25 Figure 2 shows an amino acid sequence (SEQ ID NO:4) of a partial human ADAMTS-5 protein and a nucleic acid sequence (SEQ ID NO: 3) which encodes such protein.

Figure 3 shows an amino acid sequence (SEQ ID NO:6) of a full-length human ADAMTS-6 protein and a nucleic acid sequence (SEQ ID NO:5)

30 which encodes such protein.

Figure 4 shows an amino acid sequence (SEQ ID NO:8) of a full-length human ADAMTS-7 protein and a nucleic acid sequence (SEQ ID NO:7) which encodes such protein.

Figure 5 shows an amino acid sequence (SEQ ID NO: 10) of a full-

5 length mouse ADAMTS-8 protein and a nucleic acid sequence (SEQ ID NO:9) which encodes such protein.

Figure 6 shows an amino acid sequence (SEQ ID NO: 12) of a partial human ADAMTS-8 protein and a nucleic acid sequence (SEQ ID NO: 11) which encodes such amino acid sequence.

10 Figure 7 shows an amino acid sequence (SEQ ID NO: 14), of a full-length human ADAMTS-9 protein and a nucleic acid sequence (SEQ ID NO: 13) Which encodes such protein.

Figure 8 shows an amino acid sequence (SEQ ID NO: 16) of a partial mouse ADAMTS-9 protein and a nucleic acid sequence (SEQ ID NO: 15)

15 which encodes such amino acid sequence.

Figure 9 shows an amino acid sequence (SEQ ID NO:18) of a full-length human ADAMTS-10 protein and a nucleic acid sequence (SEQ ID NO: 17) which encodes such protein.

Figure 10 show's an amino acid sequence (SEQ ID NO:20) of a partial

- 20 mouse ADAMTS-10 protein and a nucleic acid sequence (SEQ ID NO: 19) which encodes such amino acid sequence.
 - Figure 11 shows an amino acid sequence (SEQ ID NO:22) of a full length ADAMTS-R1 protein and a nucleic acid sequence (SEQ ID NO: 21) which encodes such protein.
- 25 Figure 12 depicts the cloning strategy used for isolation of a. mouse and human ADAMTS-5 cDNAs b. human ADAMTS-6 cDNA and c. human ADAMTS-7 cDNA. The domain organization of each protein relative to the cDNA clones (thin line) is shown as is the extent of overlap between clones. The original I.M.A.G.E. clones are underlined. Intronic 30 regions of incompletely spliced transcripts are shown by the angled

dotted lines. DNA scale marker (in bp) and amino acid scale marker are at upper right. Location of the probe used for in situ hybridization (ISH) is shown in a.

Figure 13 shows the predicted amino acid sequences of a. the mouse and human ADAMTS-5 proteins (alignment shows mouse sequence above, partial human sequence below) b. ADAMTS-6, and c. ADAMTS-7. The active-site sequences and proposed Met-turn are enclosed in boxes. Potential furin cleavage site(s) are indicated by arrows.

Thrombospondin type-1 modules are underlined. Potential sites for N-

- 10 inked glycosylation are overlined. Cysteine residues within the context of an MMP-like "cysteine switch" are indicated by the solid circles. Other cysteine residues are indicated by asterisks. The prodomain extends until the furin cleavage site, and the catalytic domain extends from the furin cleavage site to the approximate start
- 15 of the disintegrin-like sequence (Dis). The start of the spacer domain is indicated; the region between the N-terminal TS domain and the spacer domain is the cysteine-rich domain. The single letter amino acid code is used.

Figure 14 shows Northern analysis of expression of ADAMTS-5, 6 and 7.

- 20 RNA kilobase markers are shown at left of each autoradiogram, and tissue origin is indicated above each lane. a. Mouse embryo northern blots. b. Human multiple adult tissue northern blots.
 - Figure 15 is a schematic representation of the domain structure of ADAMTS-R1 protein as compared to ADAMTS-1 protein.
- 25 Figure 16 shows an amino acid sequence (SEQ ID NO: 24) of an alternative embodiment of a full-length human ADAMTS-10 protein and a nucleic acid sequence (SEQ ID NO: 23) which encodes such protein.

 Figure 17 shows an amino acid sequence (SEQ ID NO: 26) of an alternative embodiment of human ADAMTS-9, which is a full-length

 30 protein designated as human ADAMTS-9b and a nucleic acid sequence

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" (SEQ ID NO: 25) which encodes such protein.

Figure 18 is a schematic representation of the domain structure of human ADAMTS-9b protein as compared to human and mouse ADAMTS-9 protein.

5 <u>Detailed Description of the Invention</u> ADAMTS-N Proteins

The present invention relates to novel, isolated, substantially purified, mammalian proteins belonging to the ADAMTS subfamily of metalloproteases. As used herein, the term "substantially purified"

10 refers to a protein that is removed from its natural environment, isolated or separated, and at least 60% free, preferably 75% free, and most preferably 90% free from other components with which it is naturally associated.

The novel mammalian proteins are ADAMTS-5, ADAMTS-6, ADAMTS-7, 15 ADAMTS-8, ADAMTS-9 and ADAMTS-10, collectively ADAMTS-N. In one embodiment, the ADAMTS-5 protein is a mature mouse protein which comprises amino acid 231 through amino acid 930 of the sequence set forth in SEQ ID NO: 2. In another embodiment, the ADAMTS-5 protein is a human protein which comprises amino acid 1 through amino acid 20 518 of the sequence set forth in SEQ ID NO: 4. In one embodiment, .. ADAMTS-6 protein is a mat-Lire human protein which comprises amino acid 245 through amino acid 860 of SEQ ID NO:6. In one embodiment, the ADAMTS-7 protein is a mature human protein which comprises amino acid 233 through amino acid 997 of the sequence set forth in SEQ ID 25 NO: 8. In one embodiment, the ADAMTS-8 protein is a mature mouse protein which comprises amino acid 229 through amino acid 905 of the sequence set forth in SEQ ID NO: 10. In another embodiment, the ADAMTS-8 protein is a human protein which comprises amino acid 1 through amino acid 245 of the sequence set forth in SEO ID NO: 12. 30 In one embodiment, the ADAMTS-9 is a mature human protein which

comprises amino acid 236 through amino acid 1882 of the sequence set

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forth in SEQ ID NO: 14. In another embodiment, the ADAMTS-9 protein is a mouse protein which comprises amino acid 1 through amino acid 874 of the sequence set forth in SEQ ID NO: 16. In another embodiment, the ADAMTS-9 designated ADAMTS-9b is a human protein 5 which is comprised of 1934 amino acids as set forth in SEQ ID NO 26. In one embodiment, the ADAMTS-10 protein is a mature human protein which comprises amino acid 212 through amino acid 1081 of the sequence set forth in SEQ ID NO: 18. In another embodiment the ADAMTS- 10 protein is a mouse protein which comprises amino acid 1 . 10 through amino acid 525 of the sequence set forth in SEQ ID NO:20. In another embodiment, the ADAMTS-10 protein is a human protein which is comprised of 1072 amino acids as set forth in SEQ ID NO 24.

terminus comprise a signal sequence followed by a putative pro region
15 which contains a consensus sequence for furin cleavage (except for
ADAMTS-10), a catalytic domain, a domain of 60-90 residues with 35 to
45% similarity to snake venom disintegrins, a TS module, a cysteine
rich domain containing multiple conserved cysteine residues, a spacer
domain, and one or multiple C terminal TS modules. (See Figure 12.)
20 As determined using the BLAST software from the National Center for
Biotechnology Information, the predicted mature forms of the ADAMTS-N
proteins show an overall 20-30% similarity to each other and to
ADAMTS-1-4, although this may be considerably higher or lower for
individual domains as described below.

25 The ADAMTS-N proteins also encompass variants of the ADAMTS-N proteins shown in Figs. 1-10. A "variant" as used herein, refers to a protein whose amino acid sequence is similar to one of the amino acid sequences shown in Figs. 1-10, hereinafter referred to as the reference amino acid sequence, but does not have 100% identity with 30 the reference sequence. The variant protein has an altered sequence

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in which one or more of the amino acids in the reference sequence is deleted or substituted, or one or more amino acids are inserted into the sequence of the reference amino acid sequence. As a result of the alterations, the variant protein has an amino acid sequence which 5 is at least 95% identical to the reference sequence, preferably, at least 97% identical, more preferably at least 98% identical, most preferably at least 99% identical to the reference sequence. Variant sequences which are at least 95% identical have no more than 5 alterations, i.e. any combination of deletions, insertions or 10 substitutions, per 100 amino acids of the reference sequence. Percent identity is determined by comparing the amino acid sequence of the variant with the reference sequence using MEGALIGN project in the DNA STAR program. Sequences are aligned for identity calculations using the method of the software basic local alignment 15 search tool in the BLAST network service (the National Center for Biotechnology Information, Bethesda, MD) which employs the method of Altschul, S. F., Gish, W., Miller, W., Myers, E. W. & Lipman, D. J. (1990) J. Mol. Biol. 215, 403-410. Identities are calculated by the Align program (DNAstar, Inc.) In all cases, internal gaps and amino 20 acid insertions in the candidate sequence as aligned are not ignored when making the identity calculation.

while it is possible to have nonconservative amino acid substitutions, it is preferred that the substitutions be conservative amino acid substitutions, in which the substituted amino acid has 25 similar structural or chemical properties with the corresponding amino acid in the reference sequence. By way of example, conservative amino acid substitutions involve substitution of one aliphatic or hydrophobic amino acids, e.g. alanine, valine, leucine and isoleucine, with another; substitution of one hydroxyl-containing 30 amino acid, e.g. serine and threonine, with another; substitution of

one acidic residue, e.g. glutamic acid or aspartic acid, with another; replacement of one amide-containing residue, e.g. asparagine and glutamine, with another; replacement of one aromatic, residue, e.g. phenylalanine and tyrosine, with another; replacement of one basic residue, e.g. lysine, arginine and histidine, with another; and replacement of one small amino acid, e.g., alanine, serine, threonine, methionine, and glycine, with another.

The alterations are designed not to abolish the immunoreactivity of the variant protein with antibodies that bind to the reference protein. Guidance in determining which amino acid residues may be substituted, inserted or deleted without abolishing immunoreactivity of the variant protein with an antibody specific for the respective reference protein are found using computer programs well known in the art, for example, DNASTAR software.

The ADAMTS-N proteins also encompass fusion proteins comprising an ADAMTS-N protein and a tag, i.e., a second protein or one or more amino acids, preferably from about 2 to 65 amino acids, more preferably from about 34 to about 62 amino acids, which are added to the amino terminus of, the carboxy terminus of, or any point within 20 the amino acid sequence of an ADAMTS-N protein, or a variant of such protein. Typically, such additions are made to stabilize the resulting fusion protein or to simplify purification of an expressed recombinant form of the corresponding ADAMTS-N protein or variant of such protein. Such tags are known in the art. Representative 25 examples of such tags include sequences which encode a series of histidine residues, the epitope tag FLAG, the Herpes simplex glycoprotein D, beta-galactosidase, maltose binding protein, or glutathione S-transferase.

The ADAMTS-N proteins also encompass ADAMTS-N proteins in which 30 one or more amino acids, preferably no more than 10 amino acids, in

the respective ADAMTS-N protein are altered by posttranslation processes or synthetic methods. Examples of such modifications include, but are not limited to, acetylation, amidation, ADP-ribosylation, covalent attachment of flavin, covalent attachment of a flavin, covalent attachment of a flavin, covalent attachment of a nucleotide or a lipid, cross-linking gamma-carboxylation, glycosylation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, sulfation, and transfer-RNA mediated additions of amino acids to for the proteins such as arginylation and ubiquitination.

The ADAMTS-N proteins are immunogenic and, thus, are useful for preparing antibodies. Such antibodies are useful for identifying and diagnosing disorders which are associated with decreased expression or activity or increased expression of an ADAMTS-N protein. The 15 ADAMTS-N protein may also be useful for treating such disorder.

Diseases involving enhanced or depressed proteolyisis of the core proteins of the extracellular may involve enhanced expression or activity or decreased expression or activity of one or more ADAMTS-N proteins. Thus, ADAMTS-N proteins may be used to identify drugs,

20 polypeptides, auto-antibodies, or other natural compounds which bind to an ADAMTS-N protein with sufficient affinity to block or facilitate its activity. The activity of the ADAMTS-N protein is assayed in the presence and the absence of the putative inhibitor or facilitator using any of a variety of protease assays known in the

25 art. In general, the activity of the ADAMTS-N protein is assayed through the use of a peptide or protein substrate having a known or putative cleavage site for the ADAMTS-N protein. To detect cleavage or to monitor the extent of cleavage, the substrate is tagged in a manner which provides a detectable signal upon cleavage. For

side of the cleavage site and with a fluorescence-quenching group on the opposite side of the cleavage site. Upon cleavage by the substrate, quenching is eliminated and a detectable signal is produced. Alternatively, the substrate is tagged with a colorimetric leaving group that more strongly absorbs upon cleavage. Agents which block ADAMTS-N-catalyzed cleavage of a protein substrate may be administered to a subject to block proteolysis of the corresponding protein substrate.

ADAMTS-R1 Protein

The present invention also relates to a protein, referred to hereinafter as "ADAMTS-R1". From its amino to its carboxyl terminus, ADAMTS-R1 comprises a signal peptide sequence, a TS1 module, a cysteine-rich domain, a spacer domain, and three TS1 modules. Thus, ADAMTS-R1 has a structure which is related to or similar to an 15 ADAMTS-N protein, but which lacks a catalytic domain and a disintegrin-like domain. In one embodiment, ADAMTS-R1, protein comprises amino acid 1 through amino acid 525 of the amino acid sequence, SEQ ID NO:22, shown in Fig. 11. Such protein has a 30-40% overall sequence identity with similar regions of the ADAMTS-N 20 proteins. The ADAMTS-R1 proteins also encompass variants of the amino acid sequence shown in Fig. 11 and fusion proteins which contain the amino acid sequence shown in Fig. 11 or a variant thereof. On the basis of its domain organization, it is expected that ADAMTS-R1 can bind to extracellular matrix or cell surface 25 molecules, including ADAMTS-N substrates. Thus, it is expected that ADAMTS-R1 can be used as an cell-matrix or cell-cell adhesion molecule or an ADAMTS-N competitive inhibitor. The ADAMTS-R1 proteins are also useful for preparing antibodies. Such antibodies are useful for identifying tissues where ADAMTS-R1 is expressed and 30 for diagnosing disorders which are associated with decreased

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The present invention also provides isolated polynucleotides

expression or increased expression of. an ADAMTS-R1 protein.
Polynucleotides

which encode the mammalian ADAMTS-N proteins and the mammalian

5 ADAMTS-R1 protein. Figure 1 shows one embodiment of a
polynucleotide, SEQ ID NO: 1, which encodes the full-length mouse

ADAMTS-5 protein. Figure 2 shows one embodiment of a polynucleotide;

SEQ ID NO: 3, which encodes a partial human ADAMTS-5 protein. Figure

3 shows one embodiment of a polynucleotide; SEQ ID NO: 5, which

- 10 encodes a full-length human ADAMTS-6 protein. Figure 4 shows one embodiment of a polynucleotide; SEQ ID NO: 7, which encodes a full-length human ADAMTS-7 protein. Figure 5 shows one embodiment of a polynucleotide; SEQ ID NO: 9, which encodes a full-length mouse ADAMTS-8 protein. Figure 6 shows one embodiment of a polynucleotide;
- 15 SEQ ID NO: 11, which encodes a partial human ADAMTS-8 protein.

 Figure 7 shows one embodiment of a polynucleotide; SEQ ID NO: 13,

 which encodes a full-length human ADAMTS-9 protein. Figure 8 shows

 one embodiment of a polynucleotide; SEQ ID NO: 15, which encodes a

 partial ADAMTS-9 protein. Figure 9 shows one embodiment of a
- 20 polynucleotide; SEQ ID NO: 17, which encodes a full-length human ADAMTS-10 protein. Figure 10 shows one embodiment of a polynucleotide; SEQ ID NO: 19, which encodes a partial mouse ADAMTS-10 protein. Figure 11 shows one embodiment of a polynucleotide; SEQ ID NO: 21, which encodes a full-length ADAMTS-R1 protein.
- Due to the known degeneracy of the genetic code wherein more than one codon can encode the same amino acid, a DNA sequence may vary from that shown in SEQ ID NO: 1 and still encode an ADAMTS-5 protein having the amino acid sequence of SEQ ID NO: 2. Similarly, a DNA sequence may vary from that shown in SEQ ID NO:5, and still encode an ADAMTS-6 protein having the amino acid sequence set forth

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in SEQ ID NO:6. Similarly a DNA sequence may vary from that shown in SEQ ID NOS: 7, 9, 11, and 13, and still encode the amino acid sequences shown in SEQ ID NOS: 8, 10, 12, and 14, respectively. Such variant DNA sequence may result from silent mutations, such as for example those that occur during PCR amplification or from deliberate mutagenesis of a native sequence.

The present polynucleotides also encompass polynucleotides having sequences that are capable of hybridizing to the nucleotide sequences of FIGS 1 - 11 under stringent conditions, preferably 10 highly stringent conditions. Hybridization conditions are based on the melting temperature™ of the nucleic acid binding complex or probe, as described in Berger and Kimmel (1987) Guide to Molecular Cloning Techniques, Methods in Enzymology, vol 152, Academic Press. The term "stringent conditions, as used herein, is the "stringency" 15 which occurs within a range from about Tm-5 (5° below the melting temperature of the probe) to about 20° C below Tm. As used herein "highly stringent" conditions employ at least 0.2 x SSC buffer and at least 65° C. As recognized in the art, stringency conditions can be attained by varying a number of factors such as the length and 20 nature, i.e., DNA or RNA, of the probe; the length and nature of the target sequence, the concentration of the salts and other components, such as formamide, dextran sulfate, and polyethylene glycol, of the hybridization solution. All of these factors may be varied to generate conditions of stringency which are equivalent to the 25 conditions listed above.

The present polynucleotides also encompasses alleles of the ADAMTS-N and ADAMTS-R1 encoding sequences. As used herein, an allele or allelic sequence is an alternative form of an ADAMTS-N or ADAMTS-R1 encoding sequence which is present at the same gene locus. The 30 allele may result from one or more mutations in the ADAMTS-N or

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ADAMTS-R1 encoding sequence. Such mutations typically arise from natural addition, deletion of substitution of nucleotides in the open reading frame sequences. Any gene which encodes an ADAMTS-N protein or ADAMTS-RI protein may have none, one, or several allelic forms.

5 Such alleles are identified using conventional techniques, such as for example screening libraries with probes having sequences identical to or complementary with one or more ADAMTS-N

polynucleotides.

The present polynucleotides also encompass altered

10 polynucleotides which encode ADAMTS-N proteins, ADAMTS-R1 proteins, and variants thereof. Such alterations include deletions, additions, or substitutions. Such alterations may produce a silent change and result in an ADAMTS-N protein having the same amino acid sequence as the ADAMTS-N protein encoded by the unaltered polynucleotide. Such alterations may produce a nucleotide sequence possessing nonnaturally occurring codons. For example, codons preferred by a particular prokaryotic or eucaryotic host may be incorporated into the nucleotide sequences showing Figures 1 -11 to increase the rate of expression of the proteins encoded by such sequences. Such 20 alterations may also introduce new restriction sites into the sequence or result in the production of an ADAMTS-N or ADAMTS-RI variant. Typically, such alterations are accomplished using sitedirected mutagenesis.

The polynucleotides are useful for producing ADAMTS-N or

25 ADAMTS-R1 proteins. For example, an RNA molecule encoding an ADAMTSN protein is used in a cell-free translation systems to prepare such
protein. Alternatively, a DNA molecule encoding an ADAMTS-N protein
is introduced into an expression vector and used to transform cells.
Suitable expression vectors include for example chromosomal,

30 nonchromosomal and synthetic DNA sequences, e.g., derivatives of

SV40, bacterial plasmids, phage DNAs; yeast plasmids, vectors derived from combinations of plasmids and phage DNAs, viral DNA such as vaccinia, adenovirus, fowl pox virus, pseudorabies, baculovirus, and retrovirus. The DNA sequence is introduced into the expression 5 vector by 5 conventional procedures.

Accordingly, the present invention also relates to recombinant constructs comprising one or more of the present polynucleotide sequences. Suitable constructs include, for example, vectors, such as a plasmid, phagemid, or viral vector, into which a sequence that, 10 encodes an ADAMTS-N protein or an ADAMTS-R1 protein has been inserted. In the expression vector, the DNA sequence which encodes the ADAMTS-N protein is operatively linked to an expression control sequence, i.e., a promoter, which directs mRNA synthesis. Representative examples of such promoters, include the LTR or SV40 15 promoter, the E. coli lac or trp, the phage lambda PL promoter and other promoters known to control expression of genes in prokaryotic or eukaryotic cells or in viruses. The promoter may also be the natural promoter of the ADAMTS-N encoding sequence. The expression vector, preferably, also contains a ribosome binding site for 20 translation initiation and a transcription terminator. Preferably, the recombinant expression vectors also include an origin of replication and a selectable marker, such as for example, the ampicillin resistance gene of E. coli to permit selection of transformed cells, i.e. cells that are expressing the heterologous 25 DNA sequences. The polynucleotide sequence encoding the ADAMTS-N protein is incorporated into the vector in frame with translation

The polynucleotides encoding an ADAMTS-N or ADAMTS-R1 protein are used to express recombinant protein using techniques well known 30 in the art. Such techniques are described in Sambrook, J. et al.

initiation and termination sequences.

(1989) Molecular Cloning A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y. and Ausubel, F. M. et al. (1989) Cuurent Protocols in Molecular Biology, John Wile & Sons, New York, NY.

Polynucleotides encoding an ADAMTS-N or ADAMTS-R1 protein may

5 also be used for diagnostic purposes. The polynucleotides may be

used to detect and quantify ADAMTS-N or ADAMTS-R1 gene transcripts in

biopsied tissues in which enhanced expression or reduced expression

of the corresponding ADAMTS-N or ADAMTS-RI gene is correlated with a

disease. The diagnostic assay may be used to determine whether

expression is absent, present, or altered and to determine whether

certain therapeutic agents modulate expression of the corresponding

ADAMTS-N or ADAMTS-R1 gene.

Also encompassed by the present invention, are single stranded polynucleotides, hereinafter referred to as antisense

- 15 polynucleotides, having sequences which are complementary to the DNA and RNA sequences which encode the ADAMTS-N or ADAMTS-R1 proteins.

 The term complementary as used herein refers to the natural binding of the polynucleotides under permissive salt and 5 temperature conditions by base pairing.
- The present invention also encompasses oligonucleotides that are used as primers in polyrnerase chain reaction (PCR) technologies to amplify transcripts of the genes which encode the ADAMTS-N and ADAMTSR-1 proteins or portions of such transcripts. Preferably, the primers comprise 18-30 nucleotides, more preferably 19-25
- 25 nucleotides. Preferably, the primers have a G+C content of 40% or greater. Such oligonucleotides are at least 98% complementary with a portion of the DNA strand, i.e., the sense strand, which encodes the respective ADAM-TS family protein or a portion of its corresponding antisense strand. Preferably, the primer has at least 99%
- 30 complementarity, more preferably 100% complementarity, with such

sense strand or its corresponding antisense strand. Primers which are which have 100% complementarity with the antisense strand of a double-stranded DNA molecule which encodes an ADAMTS-N protein have a sequence which is identical to a sequence contained within the sense 5 strand. The identity of primers which are 15 nucleotides in length and have full complementarity with a portion of the antisense strand of a double-stranded DNA molecule which encodes the ADAMTS-N protein is determined using the nucleotide sequences, shown in FIG I - 11 and described by the general formula a-b; where a is any integer between 10 I and the position number of the nucleotide which is located 15 residues upstream of the 3' end of the sense or antisense strand of the cDNA sequences shown in FIG 1 -11; where b is equal to a+14; and where both a and b correspond to the positions of nucleotide residues of the cDNA sequences shown in FIGS 1 - 11.

The present invention also encompasses oligonucleotides that are useful as hybridization probes for for isolating and identifying cDNA clones and genomic clones encoding the ADAMTS-N or ADAMTS-R1 protein or allelic forms thereof. Such hybridization probes are also useful for detecting transcripts of the genes which encode the ADAMTS-N family proteins or for mapping of the genes which encode the ADAMTS-N proteins Preferably, such oligonucleotides comprise at least 210 nucleotides, more preferably at least 230, most preferably from about 210 to 280 nucleotides. Such hybridization probes have a sequence which is at least 90% complementary with a sequence 25 contained within the sense strand of a DNA molecule which encodes an ADAMTS-N protein or ADAMTS-R1 protein or with a sequence contained within its corresponding antisense strand. Such hybridization probes bind to the sense strand under stringent conditions. The term

"stringent conditions" as used herein is the binding which occurs

30 within a range from about Tin 5'C (5'C below the melting temperature

Tm of the probe) to about 20°C to 25°C below Tm. The probes are used in Northern assays to detect transcripts of ADAMTS-N homologous genes and in Southern assays to detect ADAMTS-N homologous genes. The identity of probes which are 200 nucleotides 5 in length and have 5 full complementarity with a portion of the antisense strand of a double-stranded DNA molecule which encodes the ADAMTS-N protein is determined using the nucleotide sequences shown in FIG 1 - 10 and described by the general formula a-b; where a is any integer between I and the position number of the nucleotide which is located 200 · 10 residues upstream of the 3' end of the sense or antisense strand of the cDNA sequences shown in FIG 1 -10; b is equal to a +200; and where both a and b correspond to the positions of nucleotide residues of the cDNA sequences shown in FIG 1-10.

Such probes or primers are also useful for identifying tissues 15 or cells in which the corresponding ADAMTS-N or ADAMTS-R1 gene is preferentially expressed either constitutively or at particular state of tissue differentiation or development or in disease states. Expression of the ADAMTS-N or ADAMTS-R1 gene in a particular tissue or group of cells is determined using conventional procedures 20 including, but not limited to, Northern analysis, in situ hybridization to RNA or RT-PCR amplification. Isolated polynucleotides encoding an ADAMTS-N or ADAMTS-R1 protein are also useful as chromosome markers to map linked gene positions, to identify chromosomal aberrations such as translocations, inversions 25 and trisomies, to compare with endogenous DNA sequences in patients to identify potential genetic disorders, and as probes to hybridize and thus discover novel, related DNA sequences. For use in such studies and assays, the probes may be labeled with radioisotopes, fluorescent labels, or enzymatic labels. The assays include, but are 30 not limited to, Southern blot, in situ hybridization to DNA in cells

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and chromosomes, PCR, and allele specific hybridization.

Antibodies

In another aspect, the present invention relates to antibodies which are specific for and bind to the ADAMTS-5 protein, the ADAMTS-6 5 protein, the ADAMTS-7 protein, the ADAMTS-8 protein, the ADAMTS-9 protein, the ADAMTS-10 protein, or the ADAMTS-R1 protein. Such antibodies are useful research tools for identifying *tissues that contain elevated levels of the respective protein and for purifying the respective protein from cell or tissue extracts, medium of 10 cultured cells, or partially purified preparations of intracellular and extracellular proteins by affinity chromatography. Such antibodies are also useful for identifying and diagnosing diseases associated with elevated or reduced levels of an ADAMTS-N protein or ADAMTS-R1 protein. Such antibodies are also useful for monitoring 15 the effect of therapeutic agents on the synthesis and secretion of ADAMTS-N proteins by cells in vitro and in vivo. Such antibodies may also be employed in procedures, such as co-immunoprecipitation and co-affinity chromatography, for identifying other proteins, activators and inhibitors which bind to an ADAMTS-N or ADAMTS-R1 20 protein.

The present invention also provides a method for detecting an ADAMTS-N or ADAMTS-R1 protein, in a bodily sample from a patient using antibodies immunospecific for an ADAMTS-N or ADAMTS-R1 protein. The method comprises contacting the antibody with a sample taken from the patient; and assaying for the formation of a complex between the antibody and the corresponding ADAMTS-N or ADAMTS-R1 protein present in the sample. The sample may be a tissue or a biological fluid, including but not limited to whole blood, serum, synovial fluid, stool, urine, cerebrospinal fluid, semen, diagnostic washes from trachea, stomach and other bowel segments, tissue biopsies or excised

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tissue, cells obtained from swabs and smears. To monitor changes in expression of the ADAMTS-N protein during fetal development and pregnancy, it is preferred that the sample be amniotic fluid. To monitor changes in expression of the ADAMTS-N protein during joint disorders, the preferred sample is synovial fluid. To monitor changes in expression of ADAMTS-N proteins during cancer, the preferred samples include, but are not limited to, serum, body fluids, or biopsy tissue. To monitor changes in expression of ADAMTS-N proteins during inflammation the preferred samples include, but are not limited to, serum, body fluids, or biopsy tissue.

The sample may be untreated, or subjected to precipitation; fractionation, separation, or purification before combining with the anti-ADAMTS-N protein antibody. For ease of detection, it is

preferred that isolated proteins from the sample be attached to

15 a substrate such as. a column, plastic dish, matrix, or membrane,

preferably nitrocellulose. Preferably, the detection method employs
an enzyme-linked immunosorbent assay (ELISA) or a Western immunoblot

procedure.

Interactions between an ADAMTS-N protein in the sample and the

20 corresponding anti ADAMTS-N antibody are detected by radiometric,
colorimetric, or fluorometric means, size separation, or
precipitation. Preferably, detection of the antibody-ADAMTS-N
protein complex is by addition of a secondary antibody that is
coupled to a detectable tag, such as for example, an enzyme,

25 fluorophore, or chromophore. Formation of the complex is indicative
of the presence of the ADAMTS-N protein in the test sample. Thus,
the method is used to determine whether there is a decrease or
increase in the levels of the ADAMTS-N protein in a test sample as
compared to levels of the ADAMTS-N protein in a control sample and to

30 quantify the amount of the ADAMTS-N protein in the test sample.

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Deviation between control and test values establishes the parameters for diagnosing the disease.

Preparing the ADAMTS-N proteins and the ADAMTS-R1 protein

The ADAMTS-N proteins and the ADAMT-SR1 protein may be produced 5 by conventional peptide synthesizers. The ADAMTS-N proteins and the ADAMTS-R1 protein may also be produced using cell-free translationsystems and RNA molecules derived from DNA constructs that encode an ADAMTS-N protein or an ADAMTS-RI protein. Alternatively, ADAMTS-N proteins are made by transfecting host cells with expression 10 vectors that comprise a DNA sequence that encodes the respective ADAMTS-N protein and then inducing expression of the protein in the host. cells. For recombinant production, recombinant constructs comprising one or more of the sequences which encode the ADAMTS-N protein or a variant thereof are introduced into host cells by 15 conventional methods such as calcium phosphate transfection, DEAEdextran mediated transfection, transvection, microinjection, cationic lipid-mediated transfection, electroporation, transduction, scrape lading, ballistic introduction or infection.

The ADAMTS-N protein and the ADAMTS-R1 protein may be expressed 20 in suitable host cells, such as for example, mammalian cells, yeast, bacteria, insect cells or other cells under the control of appropriate promoters using conventional techniques. Suitable hosts include, but are not limited to, E. coli, P. pastoris, Cos cells and 293 HEK cells. Following transformation of the suitable host strain and growth of the host strain to an appropriate cell density, the cells are harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract retained for further purification of the ADAMTS-N protein or the ADAMTS-R1 protein.

Conventional procedures for isolating recombinant proteins from 30 transformed host cells, such as isolation by initial extraction from

cell pellets or from cell culture medium, followed by salting-out, and one or more chromatography steps, including aqueous ion exchange chromatography, size exclusion chromatography steps, and high performance liquid chromatography (HPLC), and affinity chromatography 5 may be used to isolate the recombinant ADAMTS-N protein or ADAMTS R1 protein

Preparation of Antibodies

The ADAMTS-N proteins, and variants thereof are used as immunogens to produce antibodies immunospecific for one or more

10 ADAMTS-N protein. The term "immunospecific" means the antibodies have substantially greater affinity for one or more ADAMTS-N protein than for other proteins. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, and Fab fragments.

- Antibodies are also prepared using an oligopeptide having a sequence which is identical to a portion of the amino acid sequence of an ADAMTS-N protein. Preferably the oligopeptide has an amino acid sequence of at least five amino acids, and more preferably, at least 10 amino acids that are identical to a portion of the amino
- 20 acid sequence of an ADAMTS-N protein. Such peptides are conventionally fused with those of another protein such as keyhole limpet hemocyanin and antibody produced against the chimeric molecule. One preferred oligopeptide for preparing an antibody to mouse ADAMTS-5 has the sequence (C)HIKVRQFKAKDQTRF, SEQ ID NO: 30.
- 25 Another preferred oligopeptide for preparing an antibody to ADAMTS-5 is CEAKNGYQSDAKGVKTFVEWVPKYAG, SEQ ID NO: 3 1. One preferred oligopeptide for preparing an antibody to ADAMTS-6 has the sequence SVSIERFVETLVVADK(C), SEQ ID NO:23. One preferred oligopeptide for preparing an antibody to ADAMTS-7 has the sequence
- 30 (C) EVAEAANFLALRSEDPEKY, SEQ ID NO:24. One preferred oligopeptide for

preparing an antibody to ADAMTS-8 has the sequence

CVKEDVENPKAVVDGDWGP, SEQ ID NO:25. One preferred oligopeptide for

preparing an antibody to ADAMTS-9 has the sequence

QHPFQNEDYRPRSASPSRTH, SEQ ID NO:26. Another preferred oligopeptide

for preparing an antibody to ADAMTS-9 has the sequence

- for preparing an antibody to ADAMTS-9 has the sequence PQNCKEVKRLKGASEDGEYF, SEQ ID NO:27. One preferred oligopeptide for preparing an antibody for ADAMTS-R1 has the sequence QELEEGAAVSEEPS, SEQ ID NO:28. Another preferred oligopeptide for preparing an antibody for ADAMTS-R1 has the sequence YYPENIKPKPKLQE; SEQ ID NO:29.
- 10 Polyclonal antibodies are generated using conventional techniques by administering the ADAMTS-N protein or achimeric molecule to a host animal. Depending on the host species, various adjuvants may be used to increase immunological response. Among adjuvants used in humans, Bacilli Calmette-Guerin (BCG), and
- 15 Corynebacterium parvum. are especially preferable. Conventional protocols are also used to collect blood from the immunized animals and to isolate the serum and or the IgG fraction from the blood.

For preparation of monoclonal antibodies, conventional hybridoma techniques are used. Such antibodies are produced by continuous cell lines in culture. Suitable techniques for preparing monoclonal antibodies include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV hybridoma technique.

Various immunoassays may be used for screening to identify

25 antibodies having the desired specificity. These include protocols which. involve competitive binding or immunoradiometric assays and typically involve the measurement of complex formation between the respective ADAMTS-N protein and the antibody.

Polynucleotides that encode ADAMTS-N proteins

30 Polynucleotides comprising sequences encoding an ADAMTS-N

protein or an ADAMTS-R1 protein may be synthesized in whole or in part using chemical methods. Polynucleotides which encode an ADAMTS-N protein, particularly alleles of the genes which encode the ADAMTS-N protein, may be obtained by screening a genomic library or 5 cDNA library with a probe comprising sequences identical or complementary to the sequences shown in Figures 1 - 10 or with antibodies immunospecific for a ADAMTS-N protein to identify clones g containing such polynucleotide.

Example 1 ADAMTS-512 protein

A cDNA encoding mouse ADAMTS-5 protein was obtained using IMAGE 10 Clone 569515, purchased from Research Genetics, Huntsville, Alabama and 7 day old mouse embryo cDNA library from Clontech, Palo Alto, CA. A cDNA encoding human ADAMTS-5 protein was obtained using IMAGE Clone 345484 purchased from Research Genetics, Huntsville, Alabama 15 and a human fetal brain cDNA from Clontech. The clone inserts were sequenced in their entirety. Using oligonucleotide primers based on the sequences at the ends of the. clone inserts as template, successive rounds of RACE (Rapid Amplification of cDNA Ends) by PCR was performed at 5' and 3 ends. RACE primers were generated 50-200 20 bp from the ends of the sequences so that the contiguity of RACE clones with the I.M.A.G.E. clone could be clearly established. A single round of 5' and 3' 20 RACE sufficed for cloning of the entire coding sequence of the mouse ADAMTS-5 protein and part of the catalytic zinc binding site through to the stop codon of the human 25 ADAMTS-5 protein. Primers were designed with calculated Tm>72°C and RACE was performed with nested primers for each amplification. PCR used the Advantage PCR reagents (Clontech, Palo Alto, CA); the polymerase mix contained both Taq polymerase as well as proofreading polymerase to minimize PCR errors and employed "hot-start" PCR for 30 optimal efficiency. RACE used the following "touch-down" cycle

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conditions; 95°C for 1 minute followed by 5 cycles of 95°C for 0.5 minutes, 72°C for 5 minutes, then 5 cycles of 95°C for 0.5 minutes, 70°C for 5 minutes and 20 cycles of 95°C for 0.5 minutes, 68°C for 5 minutes. The PCR products were analyzed by Southern blotting, 5 initially using [\alpha^{32}P]-dCTP labeled.

Hybridizing bands were ligated into pGEM-T Easy (Promega, Madison, WI) and individual clones were selected by another round of Southern analysis. Automated nucleotide sequencing of both strands of each clone were done at the Molecular Biotechnology Core of the 10 Lerner Research Institute, Cleveland Clinic Foundation and nucleotide sequence data were analyzed using the DNAStar software. By integration of the overlapping sequences thus obtained, a contiguous nucleotide sequence was determined. The nucleotide sequence of the mouse ADAMTS-5 cDNA and the predicted amino acid sequence of the 15 protein encoded by this cDNA are shown in Fig. 1. The nucleotide sequence of the human ADAMTS-5 cDNA and the predicted partial amino acid sequence of the protein encoded by this cDNA are shown in Fig. 2.

The predicted molecular mass (Mr) of the mature ADAMTS-5

20 protein is 73717.50 daltons. It is expected that the actual Mr of the active ADAMTS-5 protein is different due to post-translational modification, which could potentially increase the Mr. The predicted domain organization of ADAMTS-5 protein relative to the cloned cDNA is shown in Figure 12. The pro-domain of the full-length mouse

25 ADAMTS-5 protein has 3 consensus cleavage signals for furin. The most carboxyl-terminal furin cleavage site in ADAMTS-5 predicts the processing site for generation of the mature protein The catalytic domain of the ADAMTS-5 protein contains eight cysteine residues and a reprolysin -zinc binding signature sequence, i.e., HEIGHLLGLSHD.

30 Five cysteine residues are upstream of the zinc binding sequence,

· while three residues are downstream, an arrangement that is shared with other ADAMTS members. The zinc binding signature is followed by a "Met-turn". The catalytic domain is followed by a domain with 35% similarity to snake venom disintegrins. The disintegrin domain 5 contains eight cysteine residues. The first TS repeat contains 52 _ residues and is followed by a conserved cysteine-rich sequence termed the cysteine-rich domain, designated "CRD", to distinguish it from the cysteine-free spacer domain. The CRD contains ten conserved cysteines and demonstrates high sequence homology with the CRD of 🕑 10 other ADAMTS-N proteins. The spacer domain of mouse ADAMTS-5 is 158 amino acids in length and is followed by a second TS module. ADAMTS-5 contains three potential glycosylation sites in the mature protease one of which is just upstream of the start of the spacer domain and the second lies within the spacer domain and the third is near the 15 start of the disintegrin domain. The human ADAMTS-5 protein and the mouse ADAMTS-5 protein have 96% sequence identity. ADAMTS-5 bears 46% sequence identity to ADAMTS-4 (KIAA0688), which is characterized as being involved in catabolism of aggrecan core protein in arthritis and 60% identity to ADAMTS-1 which is involved in inflammation.

20 Example 2 ADAMTS-6

The nucleotide sequence of a human cDNA encoding the fulllength ADAMTS-6 protein was obtained using IMAGE clone 742630, which
encodes EST AA400393, and a human fetal brain cDNA from Clontech.
RACE was performed as described above in Example 1. The I.M.A.G.E.

25 clone 742630 contained an ORF flanked by consensus splice sequences,
indicating the presence of introns. Two successive rounds of RACE at

the 5' end and a single round of RACE at the 3' end provided the complete coding sequence of ADAMTS-6. The putative ATG codon is within a Kozak consensus sequence and encodes the first methionine 30 within the ORF.

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The nucleotide sequence of the ADAMTS-6 DNA is shown in Fig. 3 The predicted amino acid sequence, SEQ ID NO:6, of the ADAMTS-6 protein is also shown in Fig. 3. The predicted Mr of the fulllength, unprocessed ADAMTS-6 protein is 97,115 daltons., and the 5 predicted Mr of the mature ADAMTS-6 protein is 68412.10 daltons. The domain organization of the ADAMTS-6 protein is shown in Fig. 12. The pro-domain of the full-length ADAMTS-6 protein has one consensus cleavage signal for furin. The catalytic domain of the ADAMTS-6 contains six cysteine residues and the reprolysin -zinc binding 10 signature sequence, HEIVHNFGMNHD, which is followed by a "Met-tum". The catalytic domain is followed by a domain with 35% similarity to disintegrins. The disintegrin domain contains snake venom eight cysteine residues. The first TS repeat contains 52 residues and is followed by a conserve CRD sequence which contains ten 15 conserved cysteines and demonstrates high sequence homology with the CRD of other ADAMTS proteins. The spacer domain of ADAMTS-6 is 127 amino acids in length and is followed by a second TS module. ADAMTS-6 contains four potential glycosylation sites within the pyo-domain and two in the mature protease one of which is in the cysteine rich 20 domain and the other of which is in the spacer domain. ADAMTS-6 bears 46% sequence identity to ADAMTS-1, which is involved in inflammation.

Example 3 ADAMTS-7.

The nucleotide sequence of a cDNA encoding an ADAMTS-7 protein

25 was obtained using IMAGE clone 272098, which encodes EST N4.8032, and
a human fetal brain cDNA from Clontech. RACE was performed as
described above in Example 1. The I.M.A.G.E. clone 272098 encoded a
putative pre-pro region and was extended in the 3'-direction by two
successive rounds of RACE. A typical signal peptide sequence lies

30 downstream of the first methionine in the translated ORF. This

methionine codon lies within a satisfactory Kozak consensus for translation initiation.

The nucleotide sequence of the ADAMTS-7 cDNA is shown in Fig.

4. The predicted amino acid sequence, SEQ ID NO: 8, of the ADAMTS-7 5 protein is also shown in Fig. 4. The predicted Mr of the hillalength, unprocessed ADAMTS-7 protein is 116,607 daltons, and the predicted Mr of the mature ADAMTS-7 protein is 84005 daltons. The domain organization of the ADAMTS-7 protein is shown in Fig. 12. The pro-domain of the full-length ADAMTS-7 protein has one consensus 10 cleavage signal for furin. The catalytic domain of the ADAMTS-7 protein contains eight cysteine residues and the reprolysin-zinc binding signature sequence, HELGHSFGIQHD, which is followed by a "Met-tum". The catalytic domain is followed by a domain with 30% similarity to snake venom disintegrins The disintegrin domain 15 contains eight cysteine residues. The first TS repeat contains 52 residues and is followed by a conserved CRD sequence which contains ten conserved cysteines. The spacer domain of ADAMTS-7 is 221 amino acids in length and is followed by a second TS module and a short sequence containing two cysteine residues. ADAMTS-7 contains three 20 potential glycosylation sites within the mature protease; one of which is just upstream of the spacer domain and one of which is within the spacer domain. ADAMTS-7 bears 35 % sequence identity to

Example 4: ADAMTS-8

25 enzyme.

The nucleotide sequence of a cDNA encoding a full-length, mouse ADAMTS-8 protein was obtained using IMAGE clone 1260693, which encodes EST AA855532, and a mouse embryo cDNA from Clonetech. The 30 nucleotide sequence of a cDNA encoding a partial ADAMTS-8 human

ADAMTS-1, which is characterized as being involved in inflammation

and 32% identity to ADAMTS-2 which is a procollagen processing

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protein was obtained using IMAGE clone 2119838, which encodes EST A1400905, and a human fetal brain cDNA library from Clontech. RACE was performed, as described above in Example 1. The nucleotide sequence of the cDNA encoding the full-length ADAMTS-8 mouse protein and the amino acid sequence of such protein is shown in Fig. 5. The nucleotide sequence of the cDNA encoding the partial ADAMTS-8 human protein and the amino acid sequence of such protein is shown in Fig. 6.

The predicted Mr of the full-length, unprocessed ADAMTS-8 mouse 10 protein is 1260693 daltons, and the predicted Mr of the mature ADAMTS-8 protein is 68412.10 daltons. The pro domain of the fulllength ADAMTS-8 protein has one consensus cleavage signal for furing The catalytic domain contains eight cysteine residues and the reprolysm-zinc binding signature sequence, HELGHVLSMPHD, which is 15 followed by a "Met-turn". The catalytic domain is followed by a domain with 20-30% similarity to snake venom disintegrins. The disintegrin-like domain contains eight cysteine residues. The first TS repeat is followed by a conserved CRD sequence which contains 10 conserved cysteines. The spacer domain of ADAMTS-8 is 146 amino 20 acids in length and is followed by a second TS module. The ADAMTS-8 protein contains 4 potential glycosylation sites within the mature protease: one is in the cysteine-rich domain; one is in the catalytic domain; and two are in the disintegrin-like domain. ADAMTS-8 bears 46% sequence identity to ADAMTS-1 and 42% identity to 25 ADAMTS-4.

Example 5: ADAMTS-9
The nucleotide sequence of a cDNA encoding a full-length, human
ADAMTS-9 protein was obtained using IMAGE clone 646675, which encodes
EST AA205581, and a human fetal brain cDNA from Clonetech. The
30 micleotide sequence of a cDNA encoding a partial ADAMTS-9 mouse

protein was obtained using IMAGE clone 535663, which encodes EST AAl 06215, and a mouse cDNA library obtained from Clonetech. RACE was performed as described above in Example 1. The nucleotide sequence of the cDNA encoding the full-length ADAMTS-9 human proteinand the amino acid sequence of such protein is shown in Fig.6. The nucleotide sequence of the cDNA encoding the partial ADAMTS-9 mouse protein and the amino acid sequence of such protein is shown in Fig. 7.

The predicted Mr of the mature human ADAMTS-9 protein is

10 189777.20 daltons. The prodomain of the predicted ADAMTS-9 protein
has 3 consensus cleavage signal for furin. The catalytic domain of
the ADAMTS-9 contains eight cysteine residues and the reprolysin zinc binding signature sequence, HELGHVFNMPHD, which is followed by a
"Met-turn". The catalytic domain is followed by a domain with 25-30%

15 similarity to snake venom disintegrins The disintegrin domain
contains eight cysteine residues. The first TS repeat contains is
followed by a conserved CRD sequence which. contains 10 conserved
cysteines. The spacer domain of ADAMTS-9 is 124 amino acids in
length and is followed by 14 additional TS modules and a C-terminal
20 domain. The ADAMTS-9 protein contains 6 potential glycosylation
sites within the mature protease: one in the spacer domain, one in
TSP 1 -7, one in TSPI-8, and 3 in the C-terminal domain. The ADAMTS9 bears 44% sequence identity to ADAMTS-4.

Example 6: ADAMTS-10

The nucleotide sequence of a cDNA encoding a fall-length
ADAMTS- 10 protein was obtained using IMAGE clone 110403, which
encodes EST AA588434, and a human fetal brain cDNA from Clonetech.
The nucleotide sequence of a cDNA encoding a partial, mouse ADAMTS-10
protein was obtained using IMAGE clone 1077653, which encodes EST

30 AA822090, and a mouse embryo cDNA library from Clonetech. RACE was

performed as described above in Example 1. The nucleotide sequence of the human ADAMTS-10 cDNA and the predicted amino acid sequence, SEQ ID 18, of the human ADAMTS-10 protein encoded by such DNA is shown in Fig. 9. The nucleotide sequence of the cDNA encoding the partial mouse ADAMTS-10 protein and the amino acid sequence of such protein is shown in Fig. 10.

The predicted Mr of the mature ADAMTS-10 protein is 95238

daltons. The pro-domain of the full-length ADAMTS-10 protein has no consensus cleavage signal for furin. The catalytic domain of the ...

10 ADAMTS-10 contains eight cysteine residues and the reprolysin-zinc binding signature sequence, HEIGHTFGMNHD, which is followed by a "Met-turn". The catalytic domain is followed by a domain with 30% similarity to snake venom disintegrins. The disintegrin-like domain contains eight cysteine residues. The first TS repeat is followed by a conserved CRD sequence which contains 8 conserved cysteines. The spacer domain of ADAMTS-10 is followed by 4 additional TS modules and a Kunitz domain. The ADAMTS-10 protein contains 2 potential glycosylation sites within the mature protease: one in the catalytic domain, and one in the TS 1-3 domain. ADAMTS-10 bears approximately 40% sequence identity to ADAM-TS1, which is characterized as being involved in inflammation.

Comparison of the ADAMTS-N Proteins.

As shown in Figure 11, the ADAMTS-5. ADAMTS-6, and ADAMTS-7

proteins share a common domain organization. From amino to carboxyl

25 termini, they are as follows:

1. A pre-pro region. A typical signal sequence of variable length is followed by a putative pro-region of variable length but demonstrating short stretches of sequence identity. Three cysteine residues are, predicted within each novel pro-domain, of which the
30 most C-terminal is an "asymmetric" cysteine lying within a sequence

context similar to the cysteine "switch" of the MMPs. All three novel cDNAs predict consensus cleavage signals for furin, three in the case of ADAMTS-5, and one each in the case of ADAMTS-6 and ADAMTS-7. The most carboxyl-terminal furin cleavage site in ADAMTS-5 predicts the processing site for generation of the mature protease. The amino terminus of the mature proteins is predicted to start at the residue immediately following the cleavage sites.

- 2. A catalytic domain. The catalytic domains are very similar to each other and contain eight cysteine residues and a typical
- 10 reprolysin-type zinc binding signature followed by a "Met-turn".

 Five cysteine residues are upstream of the zinc binding sequence,
 while three residues are downstream, an arrangement that is shared
 with other ADAMTS members. The methionine of the met-turn is not at
 a constant distance from the zinc-binding signature, but in all three
 15 novel proteases, a constant cysteine residue is present in that
 interval.
- 3. A disintegrin-like domain. The catalytic domain is followed by a domain of 60-90 residues with 35-45% similarity to snake venom disintegrins, but without the canonical cysteine arrangement seen in 20 the latter. This disintegrin-like domain is of comparable length in ADAMTS-5 and ADAMTS-7, it is considerably shorter in ADAMTS-6.
- 4. A TS module. The first TS repeat is very similar in all three novel proteases and very similar to the first TS repeat of other ADAMTSs. It contains the same number of residues (fifty-two) in all 25 three novel proteins.
 - 5. The cysteine-rich domain. This TS domain is followed by a conserved cysteine-rich sequence termed the cysteine-rich domain (CRD).
- 6. The spacer domain. This domain is of variable length, in all 30 ADAMTSs and lacks the sequence landmarks so characteristic of all the

other domains. It shows the least homology of all the domains.

7. A C-terminal TS module. The sequence of the second TS module is more variant between the members of the ADAMTS family than the first TS module, despite the conservation of the number and spacing 5 of cysteine residues.

Overall, the predicted mature forms of these proteases show 20-30% similarity to each other and to ADAMTS1-4 although this may be considerably higher or lower for individual domains as described above.

- ADAMTS-9 and ADAM-TS10 contain all the domains present in ADAMTS-5 through ADAMTS-8. In addition, ADAMTS-9 and ADAMTS-10 contain the following domains:
- A. ADAMTS-9: After the c-terminal TS1 domain which is present in ADAMTS5-8, ADAMTS-9 contains 13 additional and homologous 15 TS11 domains, thus, ADAMTS-9 contains a total of 15 TS1 domains, of which 14 are adjacent to each other in the c-terminal half of the molecule. The 15th TS1 domain from the N-terminus is followed by a unique c-terminal domain which does not possess recognizable domain structure and contains 196 residues including 9 cysteine residues.
- B. ADAMTS-10: After the c-terminal TS1 domain which is present in ADAMTS 8, ADAMTS-10 contains 3 additional and homologous TS1 domains, thus, that ADAMTS-10 contains a total of 5 TS1 domains, of which 4 are adjacent to each other in the c-terminal half of the molecule. The 5th TS 1 domain from the N-terminus is followed by an additional 47 amino acid residues including six (6) cysteine residues. These 47 residues have sequence similarity of 30%-40% to the c-terminus of pro-hormone convertase 5 and 6, and to the Kunitz family of inhibitors.
- Northern Analysis

 Mouse embryo northern blots and multiple tissue northern blots

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from human and mouse tissues (Clontech, Palo Alto, CA) were hybridized to the $[\alpha^{32}P]$ -dCTP labeled inserts of I.M.A.G.E. clones as per the manufacturer's recommendations followed by autoradiographic exposure for 3-7 days.

In situ hybridization used cryosections of mouse embryos of gestational age 8.5 days and 10.5 days. Embryos were collected with the inclusion of the surrounding uterus and fixed overnight in 4% paraformaldehyde. Sense and anti-sense probes continuously labeled with digoxigenin-UTP (Boehringer-Mannheim, Indianapolis, IN) were 10 transcribed with T7 and T3 RNA polymerases, respectively, using as template a 63 0 bp EcoRI-Sacl fragment from the Adamts-5 clone 569515 (Fig. 14) cloned into pBluescript SK+ (Stratagene, La Jolla, CA). In situ hybridization was done essentially as previously described in Apte, et al. (1997) J. Biol. Chem. 272:2551-25517, which is 15 specifically incorporated herein by reference, except that sections were predigested with proteinase K (Boehringer-Mannheim, Indianapolis, IN) at a lower, concentration (1 -5 μ g/ml) than reported in Apte, et al.. Bound, digoxigenin-labeled probe was detected using an alkaline phosphatase tagged anti-digoxigenin 20 antibody (Boehringer-Mannheim, Indianapolis, IN) and nuclei were

Specific hybridization of the antisense Adamts-5 probe to sections of 8.5 day-old mouse embryos was obtained, whereas only low background staining was noted with the control sense probe. Staining 25 was uniform throughout the 8.5 day old embryos. In addition, there was labeling of mRNA in trophoblastic cells lining the uterine cavity as well as in the developing placenta (Fig. 14). The decidual reaction within the uterus also showed upregulation of Adamts-5 mRNA relative to the negative controls. In sections from 10.5 day old 30 embryos, labeling was widespread but less intense compared to the 8.5

counterstained with methyl green.

day-old embryo. Labeled cells were seen in mesenchyme and somites as well as in the neural tube and developing hindgut. Northern analysis also indicated that mRNA encoding ADAMTS-5 was present in human placenta but was barely detectable in adult lung, heart, brain, 5 liver, skeletal muscle, kidney and pancreas.

Northern analysis showed undetectable expression of Adamts-6 during mouse embryo development. Northern analysis indicated that mRNA encoding ADAMTS-6 was present in human placenta but was barely detectable in adult lung, heart, brain, liver, skeletal 10 muscle, kidney and pancreas. Adamts-7 was expressed at low levels throughout mouse development. In adult human tissues examined with human cDNA probes, ADAMTS-7 mRNA was found in all tissues examined, i.e. in lung, heart, brain, liver, skeletal muscle, kidney, pancreas and placenta. The sizes of the mRNA species recognized by the probes 15 varied. ADAMTS-5 mRNA was approximately 10 kbp in size in human tissue. The most prominent Adamts-5 species was estimated at 7.5 kbp together with additional bands at 10 kbp and 4.5 kbp. The lone mRNA species detected by ADAMTS-6 probe was approximately 8.5 kbp, whereas the most common mRNA species detected by ADAMTS-7 probe 5 was 5 kbp 20 in size with an additional species seen at 7 kbp in skeletal muscle.

In mouse, ADAMTS-8 is expressed during fetal development (days 7, 11, 15, 17) and in adult mouse lung and heart with an mRNA size of approximately 3.8 kbp. In adult human tissue, ADAMTS-8 is expressed in lung and brain but not in heart, muscle, kidney, colon or thymus.

25 The mRNA size is 3.8 kbp.

ADAMTS-9 is expressed in lung, ovary placenta, heart, brain, muscle, kidney and pancreas with a mRNA size of 8 kb. In addition, kidney and ovary contain additional transcripts of size 3 kb and 4.4 kb respectively. These additional transcripts may represent 30 alternatively spliced or short forms of ADAMTS9.

ADAMTS-10 is expressed in thymus, prostate, testis, ovary, small intestine, colon, peripheral blood leukocytes, heart, brain, placenta, lung, liver, muscle, kidney and pancreas, as well as in many cell lines such as A549, HeLa and K562. There are two 5 transcripts of 5 kb and 8kb present in all tissues.

Example 7: ADAMTS-R1

The nucleotide sequence of a cDNA encoding a full-length

ADAMTS-R1 protein was obtained using IMAGE clone 752797 which encodes

EST AA, and a human fetal brain cDNA from Clontech. RACE was

10 performed as described above in Example 1. The nucleotide sequence,

SEQ ID NO:21, of the ADAMTS-R1 cDNA and the predicted amino acid

sequence, SEQ ID NO:22, of the ADAMTS-R1 protein encoded by such DNA

is shown in Fig. 11.

The predicted Mr of the full-length, unprocessed ADAMTS-R1 15 protein is 58358.20 daltons. The domain organization of the ADAMTS-10 protein is shown in Fig. 15. In contrast to the ADAMTS-N proteins of examples 1-6, ADAMTS-R1 protein does not have a prometalloprotease or disintegrin-like domain or a consensus cleavage signal for furin. ADAMTS-R1 has a signal (pre) peptide which is 20 followed by a first TS module and a conserved CRD sequence which contains 10 conserved cysteines. The spacer domain of ADAMTS-R1 is 115 amino acids in length and is followed by 3 additional TS modules and a short sequence of 33 amino acids. The ADAMTS-R1 protein contains one potential glycosylation sites which is in the spacer 25 domain. ADAMTS-R1 bears 30-40% sequence identity to ADAMTS1 and ADAMTS4 in the related domains. ADAMTS-R1 mRNA is present in human heart, brain, kidney, muscle, lung, placenta, testis, ovary, colon, intestine, and prostate. There are three transcripts of 2.5 kb, 4.7 kb and 6.5 kbp present in all such tissues. In mouse, expression is 30 seen in skeletal muscle, and the transcript size is 6.5 kb.

Although certain embodiments of this invention have been shown and described, various adaptations and modifications can be made without departing from the scope of the invention as defined in the appended claims.

5

CLAIMS

- 1. An isolated mammalian protein selected from the group consisting of an ADAMTS-5 protein an ADAMTS-6 protein, an ADAMTS-7 protein, an ADAMTS-8 protein, an ADAMTS-9 protein, an ADAMTS-10 protein, and an ADAMTS-R1 protein.
- The isolated mammalian protein of claim 1 wherein said protein 2. comprises an amino acid sequence which is at least 95% identical to a sequence selected from the group consisting of: amino acid 262 through amino acid 930 of SEQ ID NO:2; amino / 10 acid 1 through amino acid 518 of SEQ ID NO:4; amino acid 245 through amino acid 860 of SEQ ID NO:6; amino acid 233 through amino acid 997 of SEQ ID NO:8; amino acid 229 through amino acid 905 of SEQ ID NO:10; amino acid 1 through amino acid 245 of SEQ ID NO:12; amino acid 236 through amino acid 1882 of SEQ 15 ID NO:14; amino acid 1 through amino acid 874 of SEO ID NO:16; amino acid 212 through amino acid 1081 of SEQ ID NO:18; amino acid 1 through amino acid 450 of SEQ ID NO:20; and amino acid 1 through amino acid 547 of SEQ ID NO:22.
- The isolated protein of claim 2 wherein said amino acid
 sequence further comprises a prepropeptide sequence at the amino terminus thereof.
 - 4. The isolated protein of claim 1 wherein said protein is a human ADAMTS-5 protein or a mouse ADAMTS-5 protein.
- The isolated protein of claim 1 wherein said protein is a humanADAMTS-6 protein.
 - 6. The isolated protein of claim 1 wherein said protein is a human ADAMTS-7 protein.
 - 7. The isolated protein of claim 1 wherein said protein is a mouse ADAMTS-8 or a human ADAMTS-8 protein.
- 30 8. The isolated protein of claim 1 wherein said protein is a human

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10

- ADAMTS-9 or a mouse ADAMTS-9 protein.
- 9. The isolated protein of claim 1 wherein said protein is a human ADAMTS-10 or a mouse ADAMTS-10 protein.
- 10. The isolated protein of claim 1 wherein said protein is a human

 ADAMTS-R1 protein.
 - 11. An isolated polynucleotide comprising a sequence which encodes a mammalian protein selected from the group consisting of an ADAMTS-5 protein, an ADAMTS-6 protein, an ADAMTS-7 protein, an ADAMTS-8 protein, an ADAMTS-9 protein, an ADAMTS-10 protein, and an ADAMTS-R1 protein.
- The isolated polynucleotide of claim 11 wherein said protein 12. comprises an amino acid sequence which is at least 95% identical to a sequence selected from the group consisting of: amino acid 262 through amino acid 930 of SEQ ID NO:2; amino acid 1 through amino acid 518 of SEQ ID NO:4; amino acid 245 15 through amino acid 860 of SEQ ID NO:6; amino acid 233 through amino acid 997 of SEQ ID NO:8; amino acid 229 through amino acid 905 of SEQ ID NO:10; amino acid 1 through amino acid 245 of SEQ ID NO:12; amino acid 236 through amino acid 1882 of SEQ ID NO:14; amino acid 1 through amino acid 874 of SEQ ID NO:16; 20 amino acid 212 through amino acid 1081 of SEQ ID NO:18; amino acid 1 through amino acid 450 of SEQ ID NO:20, and amino acid 1 through amino acid 547 of SEQ ID NO:22.
- 13. The isolated polynucleotide of claim 11 wherein said nucleotide
 25 sequence encodes a protein having a signal sequence at the
 amino terminus thereof.
 - 14. The isolated polynucleotide of claim 11 wherein said polynucleotide comprises a sequence selected from the group consisting of: nucleotide 800 through nucleotide 2810 of SEQ ID NO:1 of an allelic variant thereof; nucleotide 1 through

30

nucleotide 1519 of SEQ ID NO:3 or an allelic variant thereof; nucleotide 754 through nucleotide 2602 of SEQ ID NO:5 or an allelic variant thereof; nucleotide 708 through nucleotide 3003 of SEQ ID NO:7 or an allelic variant thereof; nucleotide 962 through nucleotide 2992 of SEQ ID NO:9 or an allelic variant 5 thereof; nucleotide 1 through nucleotide 739 of SEQ ID NO:11 or an allelic variant thereof; nucleotide 708 through nucleotide 5648 of SEQ ID NO:13 or an allelic variant thereof; nucleotide 1 through nucleotide 2625 of SEQ ID NO:15 or an allelic variant 10 thereof; nucleotide 634 through nucleotide 3243 of SEQ ID NO:17 or an allelic variant thereof; nucleotide 1 through nucleotide 1642 of SEQ ID NO:19 or an allelic variant thereof; and nucleotide 51 through nucleotide 1625 of SEQ ID NO:21 or an allelic variant thereof.

- 15 15. The isolated polynucleotide of claim 11 wherein said polynucleotide hybridizes under stringent conditions to a nucleic acid molecule comprising a sequence complementary to the protein encoding sequence of SEQ ID NO:1; SEQ ID NO:3; SEQ ID NO:5; SEQ ID NO:7; SEQ ID NO:9; SEQ ID NO:11; SEQ ID NO:13; SEQ ID NO:15; SEQ ID NO:17; SEQ ID NO:19; or SEQ ID NO:21.
 - 16. An isolated polynucleotide having a sequence which is complementary to the protein encoding sequence of the polynucleotide of claim 11.
 - 17. An expression vector comprising a polynucleotide of claim 11.
- 25 18. A host cell transformed or transfected with an expression vector of claim 17.
 - 19. A method for producing an ADAMTS-N protein or an ADAMTS-R1 protein, said method comprising the steps of
- (a) culturing a host cell of claim 18 under conditions30 suitable for expression of an ADAMTS-N protein or an ADAMTS-R1

v 1,15,80

protein; and

- (b) recovering said ADAMTS-N protein or said ADAMTS-R1 protein from the host cell culture.
- 20. An antibody that binds to a protein selected from the group

 consisting of an ADAMTS-5 protein, an ADAMTS-6 protein, an

 ADAMTS-7 protein, an ADAMTS-8 protein, an ADAMTS-9 protein, an

 ADAMTS-10 protein and an ADAMTS-R1 protein.
- 21. An oligopeptide for producing an antibody that binds to an ADAMTS-N protein or an ADAMTS-R1 protein wherein said

 oligopeptide has a sequence selected from the group consisting of:
 - a) SVSIERFVETLVVADK, SEQ ID NO:23;
 - b) EVAEAANFLALRSEDPDKY, SEQ ID NO:24;
 - c) VKEDVENPKAVVDGDWGP, SEQ ID NO:25;
- d) QHPFQNEDYRPRSASPSRTH, SEQ ID NO:26;
 - e) PQNCKEVKRLKGASEDGEYF, SEQ ID NO:27;
 - f) OELEEGAAVSEEPS, SEQ ID NO:28;
 - g) YYPENIKPKPKLQE; SEQ ID NO:29;
 - h) HIKVRQFKAKDQTRF; and
- 20 i) CEAKNGYQSDAKGVKTFVEWVPKYAG, SEQ ID NO:30.

Fig. 1

FEATURES

Location/Qualifiers

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Fig. 2

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de gregorie

Fig. 3

FEATURES

Location/Qualifiers

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CDS

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Fig. 3 (con't)

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BASE COUNT 837 a 551 c 664 g 794 t 2 others ORIGIN 1 aatcatccag ttttctaaat tatggaaatt ttgtggaaga cgttgacctg gattttgagc 61 ctcatcatgg cttcatcgga atttcatagt gaccacaggc tttcatacag ttctcaagag 121 gaatteetga ettatettga acactaccag etaactatte caataagggt tgatcaaaat 181 ggagcatttc tcagctttac tgtgaaaaat gataaacact caaggagaag acggagtatg 241 gaccetattg atecacagea ggcagtatet aagttatttt ttaaacttte agectatgge 301 aagcactttc atctaaactt gactctcaac acagattttg tgtccaaaca ttttacagta 361 gaatattggg ggaaagatgg accccagtgg aaacatgatt ttttagacaa ctgtcattac 421 acaggatatt tgcaagatca acgtagtaca actaaagtgg ctttaagcaa ctgtgttggg 481 ttgcatggtg ttattgctac agaagatgaa gagtatttta tcgaaccttt aaagaatacc 541 acagaggatt ccaagcattt tagttatgaa aatggccacc ctcatgttat ttacaaaaag 601 tetgecette aacaacgaca tetgtatgat caeteteatt gtggggttte ggattteaca 661 agaagtggca aaccttggtg gctgaatgac acatccactg tttcttattc actaccaatt 721 aacaacaca atatccacca cagacagaag agatcagtga gcattgaacg gtttgtggag 781 acattggtag tggcagacaa aatgatggtg ggctaccatg gccgcaaaga cattgaacat 841 tacattttga gtgtgatgaa tattgttgcc aaactttacc gtgattccag cctaggaaac 901 gttgtgaata ttatagtggc ccgcttaatt gttctcacag aagatcagcc aaacttggag 961 ataaaccacc atgcagacaa gtccctcgat agcttctgta aatggcagaa atccattctc 1021 tcccaccaaa gtgatggaaa caccattcca gaaaatggga ttgcccacca cgataatgca 1081 gttcttatta ctagatatga tatctgcact tataaaaata agccctgtgg aacactgggc 1141 ttggcctctg tggctggaat gtgtgagcct gaaaggagct gcagcattaa tgaagacatt 1201 ggcctgggtt cagcttttac cattgcacat gagattgttc acaattttgg tatgaaccat 1261 gatggaattg gaaattcttg tggacgaaag gtcatgaagc agcaaaatta tggcagctca 1321 cattactgcg aataccaatc ctttttcctg gtctgcttgc agtcgagant acatcaccag 1381 ctttttagag aagtgtgtag agagctctgg tgtctcagca aaagcaaccg ctgtgtcacc 1441 aacagtatto cagcagotga ggggacactg tgtcaaactg ggaatattga aaaagggtgg 1501 tgttatcagg gagattgtgt tccttttggc acttggcccc agagcataga tgggggctgg 1561 ggtccctggt cactatgggg agagtgcagc aggacctgcg ggggaggcgt ntcctcatcc 1621 ctaagacact gtgacagtcc agcacettca ggaggtggaa aatattgeet tggggaaagg 1681 aaacggtatc gctcctgtaa cacagatcca tgccctttgg gttcccgaga ttttcgagag 1741 aaacagtgtg cagactttga caatatgcct ttccgaggaa agtattataa ctggaaaccc 1801 tatactggag gtggggtaaa accttgtgca ttaaactgct tggctgaagg ttataatttc 1861 tacactgaac gtgctcctgc ggtgatcgat gggacccagt gcaatgcgga ttcactggat 1921 atctgcatca atggagaatg caagcacgta ggctgtgata atattttggg atctgatgct 1981 agggaagata gatgtcgagt ctgtggaggg ggcggaagca catgtgatgc cattgaaggg 2041 ttcttcaatg attcactgcc caggggaggc tacatggaag tggtgcagat accaagaggc 2101 tctgttcaca ttgaagttag agaagttgcc atgtcaaaga actatattgc tttaaaatct 2161 gaaggagatg attactatat taatggtgcc tggactattg actggcctag gaaatttgat 2221 gttgctggga cagcttttca ttacaagaga ccaactgatg aaccagaatc cttggaagct 2281 ctaggtccta cctcagaaaa tctcatcgtc atggttctgc ttcaagaaca gaatttggga 2341 attaggtata agttcaatgt teccateact cgaactggca gtggagataa tgaagttgge 2401 tttacatgga atcatcagcc ttggtcagaa tgctcagcta cttgtgctgg aggtaagatg 2461 cccactaggc agcccaccca gagggcaaga tggagaacaa aacacattct gagctatgct 2521 ttgtgtttgt taaaaaagct aattggaaac atttcttgca ggtttgcttc aagctgtaat 2581 ttagcaaaag aaactttgct ttaattatat tatattccat ttgttttcaa cctcatgtaa 2641 tttgtgcaga tttgttggta aaatacatct tggcacaatg agtgtctctg ctggtgcttc 2701 toccaagact atottgaagg tgggctgttt gcctttcgtg aacacattct tggtaaagaa 2761 catcaaaagt tttaaaaaag aaaatgagca agaatcagac atcacagatg caacttcttg 2821 taatgggaga tgagaatgta cggctgtg

1.44 1.24 1.55

Fig. 4

FEATURES

source

gene

Location/Qualifiers

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CDS 13..3003

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with ThromboSpondin type I motifs-7 (ADAM-TS7) *

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PGGGSRGJVPRPSTLHGRSRPGGVSPGSVTEPGSEPGPPAAASTS
VHRGGWQQAPLGLGGWRRHLVLMGPRLPTQLLFQESNPGVHYEYT LHKLAUSHDEVFF
PVFSWHYGPWTKCTVTCGRGEKWGRHSPTCRGLVSGQGHWLQLPAHCWATTGLEVCFS
EPQFSICEMRLAIALCPRPAGRVHG*

BASE COUNT 584 a 1041 c 1003 g 590 t ORIGIN

1 ccggttcctg ccatgcccgg cggccccagt ccccgcagcc ccgcgccttt gctgcgcccc 61 etectectge tectetgege tetggetece ggegeeeceg gaccegeace aggacgtgea 121 accgagggcc gggcggcact ggacatcgtg cacccggttc gagtcgacgc ggggggctcc 181 ttcctgtcct acgagetgtg geceegegea etgegeaage gggatgtate tgtgegeega 241 gacgcgcccg ccttctacga gctacaatac cgcgggcgcg agctgcgctt caacctgacc 301 gccaatcage acctgctggc gcccggcttt gtgagcgaga cgcggcggcg cggcggcctg 361 ggccgcgcgc acatccgggc ccacaccccg gcctgccacc tgcttggcga ggtgcaggac 421 cctgagctcg agggtggcct ggcggccatc agcgcctgcg acggcctgaa aggtgtgttc 481 cageteteca acgaggaeta etteattgag eccetggaea gtgeecegge eeggeetgge 541 cacgcccagc cccatgtggt gtacaagcgt caggccccgg agaggctggc acagcggggt 601 gattccagtg ctccaagcac ctgtggagtg caagtgtacc cagagctgga gtctcgacgg 661 gagcgttggg agcagcggca gcagtggcgg cggccacggc tgaggcgtct acaccagcgg 721 tcggtcagca aagagaagtg ggtggagacc ctggtagtag ctgatgccaa aatggtggag 781 taccacggac agccgcaggt tgagagctat gtgctgacca tcatgaacat ggtggctggc 841 ctgtttcatg accccagcat tgggaacccc atccacatca ccattgtgcg cctggtcctg 901 ctggaagatg aggaggagga cctaaagatc acgcaccatg cagacaacac cctgaagagc 961 ttctgcaagt ggcagaaaag catcaacatg aagggggatg cccatcccct gcaccatgac 1021 actgccatcc tgctcaccag aaaggacctg tgtgcagcca tgaaccggcc ctgtgagacc 1081 ctgggactgt cccatgtggc gggcatgtgc cagccgcacc gcagctgcag catcaacgag 1141 gacacgggcc tgccgctggc cttcactgta gcccacgagc tcgggcacag ttttggcatt 1201 cagcatgacg gaagcggcaa tgactgtgag cccgttggga aacgaccttt catcatgtct 1261 ccacagetee tgtacgacge egeteceete acetggteee getgeageeg ceagtatate 1321 accaggitee tigacegigg giggggeetg tgeetggacg acceteetge caaggacatt 1381 atogactice coteggtgcc acctggcgtc ctctatgatg taagccacca gtgccgcctc 1441 cagtacgggg cctactctgc cttctgcgag gacatggata atgtctgcca cacactctgg 1501 tgctctgtgg ggaccacctg tcactccaag ctggatgcag ctgtggacgg cacccggtgt 1561 ggggagaata agtggtgtct cagtggggag tgcgtacccg tgggcttccg gcccgaggcc 1621 gtggatggtg gctggtctgg ctggagcgcc tggtccatct gctcacggag ctgtggcatg 1681 ggcgtacaga gcgccgagcg gcagtgcacg cagcctacgc ccaaatacaa aggcagatac 1741 tgtgtgggtg agcgcaagcg cttccgcctc tgcaacctgc aggcctgccc tgctggccgc 1801 ccctccttcc gccacgtcca gtgcagccac tttgacgcta tgctctacaa gggccagctg 1861 cacacatggg tgcccgtggt caatgacgtg aacccctgcg agctgcactg ccggcccgcg 1921 aatgagtact ttgccaagaa gctgcgggac gccgtggtcg atggcacccc ctgctaccag 1981 gtccgagcca gccgggacct ctgcatcaac ggcatctgta agaacgtggg ctgtgacttc 2041 gagattgact ccggtgctat ggaggaccgc tgtggtgtgt gccacggcaa cggctccacc 2101 tgccacaccg tgagcgggac cttcgaggag gccgagggtc tgggggtatgt ggatgtgggg 2161 ctgatcceag cgggcgcacg cgagatccgc atccaagagg ttgccgaggc tgccaacttc 2221 ctggcactgc ggagcgagga cccggagaag tacttcctca atggtggctg gaccatccag 2281 tggaacgggg actaccaggt ggcagggacc accttcacat acgcacgcag gggcaactgg 2341 gagaacctca cgtccccggg tcccaccaag gagcctgtct ggatccaggt gcctgcctcc 2401 cgtggcccag gcggggggag cagaggcgga gtccccaggc ccagcaccct ccatggcagg 2461 tctcgtcctg gaggagtgag ccctggttca gtcacagagc ctggctctga gccaggccct 2521 cctgctgcgg cctctacctc agtttcccca tctttaaaat ggcccaatct tgtagctgca 2581 gttcacagag gtggctgggg tcaagctcct ttaggactgg gtggatggag aagacacctt 2641 gtgctcatgg gcccccgcct gcccacccag ctgctgttcc aggagagcaa ccctggggtg 2701 cactacgagt acaccatcca cagggaggca ggtggccacg acgaggtccc gccgcccgtg 2761 ttctcctggc attatgggcc ctggaccaag tgcacagtca cctgcggcag aggtgagaag 2821 tggggcaggc acagccccac ctgcaggggc ttagtgtctg gacagggaca ctggcttcag 2881 ctcccagctc actgctgggc caccacgggt ttggaagttt gcttctctga gcctcagttc 2941 tecatetgtg agatgagget agegattgee etgtgteeca ggeeegetgg gagggtacat 3001 ggatgaggca ggtgggtgct ggctcgcggc gcatgttcag tgtgctccag ctcttggcgt 3061 teteceteca ggggacacag etececeteg atagaccagt ccagtggeec eteaceacac 3121 tgacttattt ccctaaacta tttataaaaa gtagggcaat ttcattaact ctgactctta 3181 cctgcccggg cggccgctcg agccgagtaa tcactagt

Fig. 5A

10	20	30	40	50	60 .	70
سيلسيس		لسيلس	سيليب	Huuluu	لسيليين	
tagggcgactgcac	gggacgcgcgg	aggacgcgc	gctcgcgg	cccggggcgcc	cacgtgctcgagt	tctg 70
ctaggttggctggc	gcaggaggagcg	ggctgcgcg	atccagag	gggccgccagg	gaccgccgcgc	cacgt 140
gccgctagccgagt	cggcctccccat	ccgattgat	catttttc	ctggacagago	cgacccggccgc	ctcgg 210
gccaccagcacctg	cccgcgcgcgg	gatcttctt	ccctctcc	cgcgctccgca	agcactctgccc	CCATG 280
CTCCGCGACCCCAC	CACCACCGGGTC	GCCGCCCT	CCIGCIGC	TGCTATTGCAC	SCIECCECCCC	SCCAC 350
360	370	380	390	400	410 ·	420
سيلسيس			سلسب	سلسبل	ليتتلتين	
TOGICIGOGGAGOO	000000000000000000000000000000000000000	GGAACCGGG	GCGCAGGC	CTCGGAGCTAC	FIGGIGCCCACG	CGGTT 420
GCCCGGCAGCGCGA	GCGAGCTCGCCT	TCCACCTGT	CCGCCTTC	GGCCAGGGCT.	regreereece	TGGCG 490
CCTGACGCCAGCTT	CCTGGCGCCGG	ATTCAAGAT	CGAGCGCC	TOGGGGGGTC	CAGCCCCCCCCCC	cacac 560
GCGAGCCGGGACTG	CGTCCCTCCTT	CTTCTCTGGC	'ACAGTGAA	TGGAGAACGG	GAGTCGCTGGCG	GCGAT 630
GAGCTGTGTCGCGG	GCTGGAGCGGC	regrictiee	TGGCAGGC	GAGGAGTTCA	CATCCAGCCAC	AGGGC 700
710	720	730	740	750	760	770
سيلسيس			سلسب	سلسب	لسبلست	
GCTGCGGACTCCCT	GGACCAGCCIC	ATCGCCTGCA	GCGCTGGC	CGCCGGGACA	GCGCCGCGAAGA	CCCCG 770
GCCICCCICCCCCCC	GAAGTTTTCCC	CCTCCCTCAA	GGACTGG	GIGGGAGGIG	GAGATGGGTAAT	GGGCA 840
GCGACAGGAGAGAZ	GIGACAACGAA	GAGGACAGGA	AGCAGGAC	CAAGGAGGGGT	TCCTCAAAGAGA	CAGAA 910
GACTOCOGCAAAGI	GCCACCACCCT	ICGGATCCAA	AACTAGAZ	CCAAGAGGTT	TGTGTCCGAGGC	TCGCT 980
TCGTGGAAACACTT	CIGGIGGCIGA	IGCGICCATC	GCTGCCT.	CTATEGGACO	GACCIGCAGAAC	CACAT 1050
1060	1070	1080	1090	1100	1110	1120
سلسلسن			سلسب	ستلينتان	ليتبليين	
CCTCACCGTGATG	CAATGGCAGCC	CGAATCTACA	AGCACCC	EAGCATCAGGA	ACTCCGTCAACC	TIGIG 1120
GIGGIGAAAGIGC	LAATAGIGGAAA	AAGAAAGATO	3GGGCCCGC	CAAGIGICCGA	CAACGGGGGGCT	CACAC 1190
TGCGCAACTTCTGC	CAGCTGGCAACG	GCGTTTCAAC	CAAGCCCA	FIGACCGCCAC	CCGGAGCACTAT	GACAC 1260
TGCCATCTTGTTC	ACCAGACAGAAC	TICIGIGGG	AAGGGAGA(CAGIGIGACA	CCCTGGGGATGG	CAGAC 1330
GITGGCACCATCTO	FIGACCCCGACA	AGAGCIGCIO	CAGIGATO	AAGGATGAGGG	ACTGCAGGCAGC	CTACA 1400
1410	1420	1430	1440	1450	1460	1470
سيلسيلسد		سياس	سلسب	بئيلينيلين	لتتبليتيل	
CCCTGGCCCATGA	CTAGGGCACGI	TCTCAGCATO	CCCCATG	ATGATICTAAG	CCCIGIGIGAGA	ATTGIT 1470
TEGECCCATEGGC	AAGTACCACATC	ATGGCGCCAT	TTCTTCAT	CACGIGAACA	AGACGCTGCCCT	GGTCT 1540
CCCTGCAGTGCTG	ICTACCICACAC	AGCTCCTGG	ATGATGGT	CACGGAGATIC	FICTICTGGATGO	CCCCA 1610
CCTCCGTTCTCCC	CCTCCCCACAGG	ECTCCCGGG	CCACAGCA	CCCTCTACGAC	CIGGACCAGCA	FIGCAA 1680
GCAGATCTTTGGG	CCIGATITCCGA	CACTGCCCC	AACACCTC	TGTGGAGGACA	ATCIGIGICCAGO	CICIGI 1750

9/54 Fig. 5A (con't)

1760 	1770 	1780	1790	1800	1810	1820
GCCCGTCATCGGGATZ						
CACCCIGIGGCCCTGC						
GGCTGTGGTAGATGG						
ATACAATTCTCGAACC						
GAGTCAAGTACCAATC						
2110	2120	2130	2140	2150	2160	2170
TGAGAAATATAATGCC						
GGAGTGTCCCCCCGAC	BACCATICA A		CSCATILICO	STACCACTICA(TTCA 21/0
AAGCTAAGGTGATCGZ						
TAAGGCTGGCTGTGAC						
GCCACTGCCTGTAGG						
2460	2470	2480	2490	2500	2510	2520
لسلسلسل	· · •					
TCCCAGCIGGIGCCAC						
CCTGGCGCTGAAGACA						
GACATCITGGTGAAGC						
TCCAGGCCCTGCCTGA						
CAGATATACCTTCTTT	GICCCCAATC	ACATGGACTTC	AGCGTGCAGA	ATAGCAAGG	AAAGAGCAAC	7800 2800
2810	2820	2830	2840	2850	2860	2870
ليسلسلسل						
AACATCATTCAGTCAC						
GAGGTAGCTGGCAGCG	GCGGACTGTG	GAATGCAGGA	CCCTCACCT			MCA 2070
GGCTCTGAAACCTGAC	GATGCCAAGC	CCTGTGGAAGC	CAGCCGTGTC	CCCCtcatc	ccettaata	1322 3010
tctcttaggcttatgg	atttgggcta	.ctqqtqtaaca	gacaaaggto	ccctccaaoo	stoatactaca	stat 3080
caagatggcacggccc	tttcaggcct	tctattactac	aaccccttoo	rotactaccta	attcataacc	maag 3150°
3160	3170	3180	3190	3200	3210	3220
السلسلسل						3220 l
agagaagagggtataa						
agaagtcgggataggt						
tttgcaaaggactagc						
aatctacctcacagcg						
agcaagctccataggt	atctccaago	tatcttcagaa	atgtccgtgg	ctgttttcag	rtattaaaato	etgt 3500

Fig. 5A (con't)

3510 3520 3530 3540 3550 3560 3570

tgtctaaaagggcagcagtgtccatcacagggttatagaaagccacttttctcaggctgccacctgctgg 3570
ggcggacccatttcaagtatttatgcaaatatgtctccgaactaaagtgtgtcttacaccaaaagngc 3638

MOUSE HDAM 758 10 MLRDPTTTGWPPLLLLLLQLPPPPLVCGAPAGPGTGAOAS 40 ELVVPTRLPGSASELAFHLSAFGQGFVLRLAPDASFLAPE 80 FKIERLGGSSAAAGGEPGLRGCFFSGIVNGERESLAAMSC 120 VAGWSGSFILLAGEEFTIQPQGAGDSLDQPHRLQRWGPGQR 160 REDPGLAAAEVFPLPQGLEWEVEMGNGQGQERSDNEEDRK 200 210 220 230 N-terminus of mature QDKEGLLKETEDSRKVPPPFGSKTRSKRFVSEARFVETLL 240 VADASMAAFYGIDLONHILIVMSMAARIYKHPSIRNSVNL 280 WVKVLIVEKERWGPEVSDNGGLTLRNFCSWQRRFNKPSD 320 RHPEHYDTAILFIRONFOGKGEOCDILGMADVGTICDPDK 360 SCSVIKDEGLQAAYTLAHELGHVLSMPHDDSKPCVRLFGP 400 410 420 430 440 _____ MGKYHMMAPFFIHVNKILPWSPCSAVYLITELLDDGHGDCL 440 LDAPTSVLPLPTGLPCHSTLYELDOOCKOIFGPDFRHCPN 480 TSVEDICVQLCARHRDSDEPICHTKNGSLLWADGTPCGPG 520 8 4 HLCLDGSCVLKEDVENPKAVVDGDWGPWRPWGOCSRTCGG 560 GIQFSNRECDNPMPQNGGRFCLGERVKYQSCNTEECPPNG 600 610 620 630 640 KSFREQQCEKYNAYNH FDLDGNFLQWYPKYSGVSPRDRCK 640 LFCRARGRSEFKVFEAKVIDGILCGPDILSICVRGQCVKA 680 10 CY GCDHVVNSPKKLDKCGVCGGKGTACRKISGSFTPFSYGYN 720 spacer ~146aa DIVTIPAGATNIDVKORSHPGVRNDGSYLALKTANGOYLL 760 NGNLAISAIEQDILVKGTILKYSGSMATLERLQSFQALPE 800 810 820 830 840 PLTVQLLTVSGEVFPPKVRYTFFVPNDMDFSVQNSKERAT 840 INTIQSLPSAEWVLGDWSECPSTCRGSWORRTVECRDPSG 880 QASDICDEALKPEDAKPCGSQPCPL 905

Fig. 6A

	CATAL	YTIC L	SomAIN,	ADAm	TS-8	(HUMAN).	
10	20	30	40				
بانتيانيينانين	لتتنبلين	بيليين	للتثبليا			·	
CGAGGGCAGAAGGCGC	TAGOGAGOO	GCCACCG(CCCTCCC	40			
GCCACGAGTAGGACC	'AAGCGGTTTV	GIGICIG	AGGCGCGC	80			
TTCGTGGAGACGCTGC	TOGTGGCCG	ATGCGTC	CATGGCTG	120			
CCTTCTACGGGGCCGA	CCTCCAGAA	CCACATO	CIGACGIT	160			
AATGTCTGTGGCAGCC	CGAATCTAC	AAGCACC	CAGCATC	200			
210	220	230	240				•
			لسبب				
AAGAATTCCATCAACC	TGATGGTGG	TAAAÀGI	CIGATOG	240		•	
TAGAAGATGAAAAATC						•*	0)=
GGGCTTACACTGCGT	AACTTCTGC	AACTGGC	AGCGGCGT	320	•		
TICAACCAGCCCAGCC	ACCGCCACC	CAGAGCA	CTACGACA	360			
CGGCCATCCTGCTCAC	CAGACAGAA	CTTCTGT	GGCAGGA	400			**
410	420	430	440)			***
	لبينانين	•	لسيبات				
GGGGCTGTGTGACACC	CICCGIGIC	GCAGACA'	TOGGGACC	440			•
ATTTGTGACCCCAAC							
AGGGCTCCAGGCGG					•		
GCACGTCCTCAGCATO							
ACACGGCTCTTCGGG	CCATGGGCA	AGCACCA	CGTGATGG	600			
610	620	630	640)			
			لسياس				
CACCGCTGTTCGTCC	ACCTGAACCA	GACGCIG	CCCIGGIC	640			
CCCTGCAGCGCCAT							
TGGATCCATTTCAAG							
TAAAGIGIGATCITA'							

HUMAN ADAM-TSSI CATALYTIC DOMAIN

10 Mahue professe FUSEAR	
RAEGASEPPPPLGATSRTKREVSEARFVETLLVADASMAA 40	
FYGADLQNHILILMSVAARIYKHPSIKNSINLMVVKVLIV 80	
EDEKWGPEVSDNGGLTLRNFCNWQRRFNQPSDRHPEHYDT 120	,
AILLIRQNFCGQEGLCDILGVADIGIICDPNKSCSVIEDE 160	
GLQAAHTLAHELGHVLSMPHDDSKPCTRLFGPMGKHHVMA 200	
210 220 230 240	
<u> </u>	
PLFVHLNQTLFWSPCSAMFSGCHLQGWTHFKYLCKCVSEL 240	

Fig. 6B

Fig. 7A

Fig. 7A (con't)

1760 1770 1780 1790 1800 1810 1820	
	1000
CTGCAACACGGAGCCATGTCTCAAGCAGAAGCGAGACTTCCGAGATGAACAGTGTGCTCACTTTGACGGG	
AAGCATTTTAACATCAACGGTCTGCTTCCCAATGTGCGCTGGGTCCCTAAATACAGTGGAATTCTGATGA	
AGGACCGGICCAAGITGITCIGCAGAGICGCAGGGAACACAGCCTACTATCAGCTITCGAGACAGAGIGAT	
AGATGGAACTCCTTGTGGCCAGGACACAAATGATATCTGTGTCCAGGGCCTTTGCCGGCAAGCTGGATGC	
GATCATGITTTAAACTCAAAAGCCCGGAGAGATAAATGCGGGGTTTGTGGTGGCGATAATICITCATGCA	2100
2110 2120 2130 2140 2150 2160 2170	
AAACAGIGGCAGGAACATTTAATACAGIACATTATGGTTACAATACIGIGGTCCGAATTCCAGCIGGIGC	
TACCAATATTGATGTGCGCAGCACAGTTTCTCAGGGGAAACAGACGATGACAACTACTTAGCTTTATCA	
AGCAGTAAAGGTGAATTCTTGCTAAATGGAAACTTTGTTGTCACAATGGCCAAAAGGGAAATTCGCATTG	
GGAATGCTGTGGTAGAGTACAGTGGGTCCGAGACTGCCGTAGAAAGAA	2380
GCAAGAACTTTTGCTTCAGGTTTTGTCGGTGGGAAAGTTGTACAACCCCGATGTACGCTATTCTTTCAAT	2450
2460 2470 2480 2490 2500 2510 2520	
ATTCCAATTGAAGATAAACCTCAGCAGITTTACTGGAACAGTCATGGGCCATGGCAAGCATGCAGTAAAC	2520
CCTGCCAAGGGGAACGGAAACGAAAACTTGTTTGCACCAGGGAATCTGATCAGCTTACTGTTTCTGATCA	2590
AAGATGCGATCGGCTGCCCCAGCCTGGACACATTACTGAACCCTGTGGTACAGGCTGTGACCTGAGGTGG	2660
CATGTTGCCAGCAGGAGTGAATGTAGTGCCCAGTGTGGCTTGGGTTACCGCACATTGGACATCTACTGTG	2730
CCAAATATAGCAGGCTGGATGGGAAGACTGAGAAGGTTGATGATGGTTTTTGCAGCAGCCATCCCAAACC	2800
2810 2820 2830 2840 2850 2860 2870	
	_
AAGCAACCGIGAAAAATGCTCAGGGGAATGIAACACGGGIGGCTGGCGCTATTCTGCCTGGACTGAATGT	2870
TCAAAAAGCTGTGACGGTGGGACCCAGAGGAGAAGGGCTATTTGTGTCAATACCCGAAATGATGTACTGG	
ATGACAGCAAATGCACACATCAAGAGAAAGTTACCATTCAGAGGTGCAGTGAGTTCCCTTGTCCACAGTG	
	3080
CAGTTTGGTGAAGATCGATTAAATGATAGAATGTGTGACCCTGAGACCAAGCCAACATCTATGCAGACTT	
3160 3170 3180 3190 3200 3210 3220	
GICAGCAGCCGGAATGTGCATCCTGGCAGGCGGGTCCCTGGGTACAGTGCAGTGTCACTTGTGGACAGGG	3220
ATACCAGCTAAGAGCAGTGAAATGCATCATTGGGACTTATATGTCAGTGGTAGATGACAATGACTGTAAT	
GCAGCAACTAGACCAACTGATACCCAGGACTGTGAATTACCATCATGTCATCCTCCCCCAGCTGCCCCGG	
	3430
CACITGIGGGAAAGGTACCCGGATGAGATACGICAGCIGCCGAGATGAGAATGGCICIGIGGCIGACGAG	

Fig. 7A (con't)

	3510	3520	3530	3540	3550	3560	3570
ىلىس	بليسليين		عليتبيلين	نلىسلىن	 	بلينيلين	
AGTGCC	TGTGCTACCC	TGCCTAGACC	AGTGGCAAAG	GAAGAATGIT	CIGIGACACO	CIGIGGGCAA	NGGA 3570
AGGCCT	MGGACTGGAG	CICTICCICI	GIGACCIGIG	GCAAGGTAG	GGCAACCCGG	CAAGIGAIGI	GIGT 3640
CAACTA	ACAGTGACCAC	GTGATCGATO	GGAGIGAGIG	IGACCAGGAT	TATATCCCAG	AAACTGACCA	GGAC 3710
TGTTCC	CATGICACCAT	GCCCTCAAAG	CACCCCAGAC	AGTGGCTTAG	CICAGCACCO	CITCCAAAAT	GAGG 3780
ACTATO	CGTCCCCGGAG	CCCAGCCCC	AGCCGCACCC	ATGTGCTCGG	TGGAAACCAG	TGGAGAACTG	GCCC 3,850
	3860	3870	3880	. 3890	3900	3910	3920
بليبيد	ىلىسىلىس	بليتيلين	بليندلين	بلتنتلين	ىلىنىلىن	بليسلين	
CIGGG	SAGCATGITCC	AGTACCIGIG	CTGGCGGATC	CCAGCGGCGI	GITGITGIAT	GTCAGGATGA	AAAT 3920
GGATAC	CACCGCAAACC	ACTGTGTGGA	CAGAATAAAA	CCIGAIGAGC	AAAGAGCCTG	TGAATCCGGC	CCIT 3990
GICCIC	CAGTGGGCTTA	TGGCAACTGG	GGAGAGTGCA	CTAAGCTGTG	TGGTGGAGGC	ATAAGAACAA	GACT 4060
GGIGG	ICIGICAGCO	FICCAACGGIG	AACGGTTTCC	AGATTTGAGC	TGTGAAATTC	TTGATAAACC	TCCC 4130
GATCG	IGAGCAGIGIA	ACACACATGO	TTGTCCACAC	GACGCIGCAI	GGAGTACTGG	CCCTTGGAGC	TCGT 4200
	4210	4220	4230	4240	4250	4260	4270
للبيي	ىلىسىلىس	ىلىسىلىن	بلينيلين	<u></u>	ىلىنىلىن	بليتيلين	
GITCI	GICTCTTGTG	FICGAGGGCAT	'AAACAACGAA	ATGITTACIC	CATGGCAAAA	GATGGAAGCC	ATTT 4270
AGAAA	JIGATTACIGI	CAAGCACCTGG	CTAAGCCACA	TGGGCACAGA	AAGTGCCGAG	GAGGAAGATG	xcccc 4340
AAATG	GAAAGCTGGCC	CTTGGAGTCA	GICCICIGIG	TCCTGTGGCC	GAGGCGTACA	GCAGAGGCAT	GIGG 4410
GCTGT	CAGATOGGAAO	CACACAAAATA	CCCAGAGAGA	CCGAGTGCAA	CCCATACACC	'AGACCGGAG'I	CCGGA 4480
ATGCG	AATGCCAAGG	CCACGGIGIC	CCCTTTACAC	TTGGAGGGCA	GAGGAATGGC	'AAGAATGCAC	CAAG 4550
	4560	4570	4580	4590	4600	4610	4620
لبيب	السياسي	ىلىنىلىنى	بليبيلين	ىلىسىلىن	بليسلين	لسلساني	
ACCTG	CGGCGAAGGC	CCAGGTACCC	CAAGGIGGIG	TGIGIGGAT	ACAACAAAAA	CGAGGTGCAT	reege 4620
CACGC	TGTGACGTGAC	CAAGCGGCCC	CICGACCCIC	AAAGCTGTAC	TITIGCAACCC	TGCGAGTATC	FICIG 4690
GATCA	CAGGAGAATG	FICAGAGIGCI	CAGIGACCIG	TGGAAAAGG	TACAAACAA	GCTTGTCTC	CGICC 4760
AGCGA	GATITACACC	GGAAAGAGAA	TATGAATAC	'AGCTACCAA?	CCACCATCA	CIGCCCAGGC	CACGC 4830
AGCCC	CCCAGIGITC	ACCCCTGTTAC	CIGAGGGAGI	GCCCIGICIC	CGCCACCIGC	AGAGTTGGC	ACTG 4900
	4910	4920	4930	4940	4950	4960	4970
للبيب	لسلسل	ىلىسىلىس	بلينيانين	<u> ئىنتىلىن</u>	بليبيلين	لسسلس	
GGGGA	GCTGCTCAGT	GICTIGICGI	TTGGAGTGAT	CCAGAGATC:	IGIGCAAIG t	taaccaatga	aggac 4970
caacc	cagccactta	tgccacactga	atctgaagcca	gaagaacgaa	aaaacctgccg	gtaatgtctat	taact 5040
gtgag	ttaccccaga	attgcaaggag	gtaaaaagac	ttaaaggtgo	ccagtgaagat	ggtgaatati	FECCE 2110
gatga	ttagaggaaa	gcttctgaaga	atattctgtgc	ggggatgcad	ctctgaccacc	ccaaagagta	acara pren
acact	ggtgcatgga	gactctgagaz	atttctccgag	gtttatggg	cacaggttaca	acaACCCAAC	AGAAT 5250

Fig. 7A (con't)

	5260	5270	5280	5290	5300	5310	5320
ىلىسى	سسسسه	سسسلس	عليسلين	سلسسلت	بطبيبيلين	سلسسلت	ш
GICCCI	L'ATAACGGGAG	CCGGCGCGAT	GACTIGCCAATO	JICGGAAGGA'I	TACACGGCCC	CIGGGITTIC	CAG 5320
TTTTC	AGAAAATCAGA	ATAGACCTGA	CAGCATGCAC	CATAATCACCA	ACTGACTTACA	GTTTGCAAGC	ACA 5390
AGCGAZ	AGGACATOCCG	TCCCTTTTGC	CACAGCCGGGC	GATTGCTACAC	CGCTGCCAAC	FIGCCCACAGO	EGTC 5460
GTTTT	AGCATCAACCT	TTATGGAACC	ECTIGICITY	[AACTGAATC]	TGCCAGATGGA	TATCACAAGC	GAA 5530
TTATC	CTGTCTCTGAC	ATCAAGAAGT	CCCCGGATGGT	PACCOGAGIO	TAGGGAAATC	CCCTCCTTAC	TGT 5600
	5610	5620	5630	5640	5650	5660	5670
ىلىبىد	undund	سسسس	ببلسيبلين	سلسسلس	سلسسلس	بالبيباب	
GGAAAZ	ATGCACTCCAT	CCTCTGGTAC	recectegae:	FIGCGAGITITI	TATAGCTAAGG	TIGCTTTGAAC	EAGG 5670
AAGCC	ATTATGGATGG	ATGAAGGATA	TAATGCAATA	ACCTCCACCTT	PARTITOGGIC	CATGIGIATO	FIGT 5740
GIGIGI	GITIGIGIGI	GACTIGIATO	TIGIGIGIG	CAAATGTGTGT	ACATATACAT	ATATACA 58	304

Fig. 7B

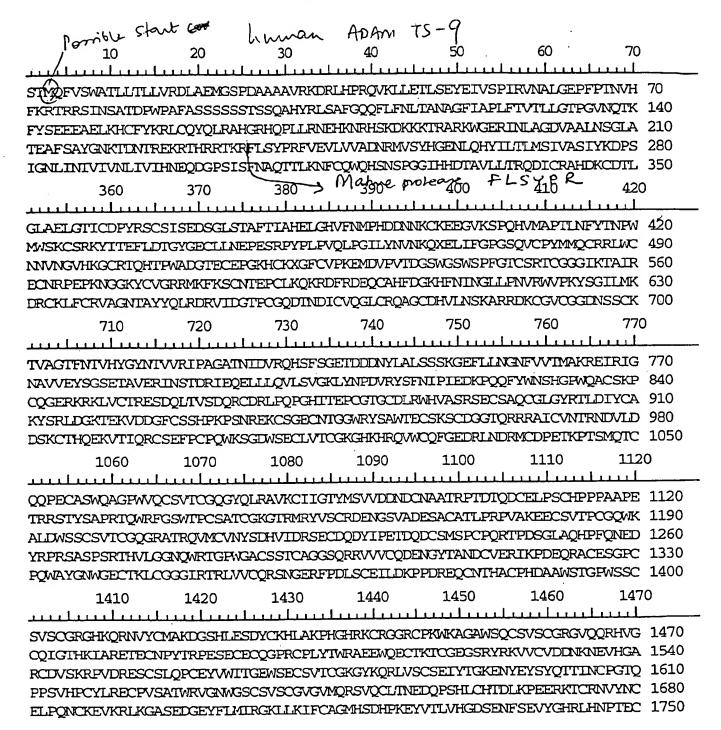


Fig. 7B (con't)

	1760	1770	1780	1790	1800	1810	1820
ىلىسىد	ىلىرىللىن	ليسلسب	لبييليين	سسلست	ليسليسا	ليبيلينيا	
PYNGSF	RDDCQCRKDY	TAAGFSSFQ	KIRIDLISMQ	IITTDLQFA	RTSEGHPVPFA	TAGDCYSAAK	CPQGR 1820
FSINLY	GIGLSLTES!	RWISQGNYA	VSDIKKSPDG	TRVVGKCGG:	ZCGKCTPSSGI	GLEVRVL.LR	CFEEE 1890
AIMDG.	RIVMOYLHLI	ILGACVCVCV	FVCDLYACVC	KCVYIYIYT	1934		

Fig. 8

ORF=2 HTAVISLCSGMMGTFRSHDGDYFTEPLOSVDDQEDEEEON 40 mahne ADAMTS9 KPHITYRHSTPOREPSTGKHACATSELKNSHSKDKRKIRM 80 RKRRKRNSLADDVALLKSGLATKVLSGYSNOINVIRDRWN 120 FLSYPRF ... HKRTKRFLSYPRFVEVMVVADHRMVLYHGANLQHYILIILM 160 Mouse Apam-759 pout-al sequence (see figure SIVASIYKDSSIGNLINIVIVNLVVIHNEQEGPYINFNAQ 200 TTLKNFCQWQHSKNYLGGIQHDTAVLVTREDICRAQDKCD 240 TLGLAELGTICDPYRSCSISEDSGLSTAFTIAHELGHVFN 280 MPHDDSNKCKEEGVKSPQHVMAPILNFYINFWMWSKCSRK 320 YITEFIDIGYGECLINEPASRTYPLPSQLPGLLYNVNKQC 360 ELIFGPGSQVCPYMMQCRRLWCNNVDGAHKGCRTQHTPWA 400 DGTBCEPGKHCKFGFCVPKEMBGPAIDGSWBGWSHFGTCS 440 RICGGGIKTAIRECNRPEPKNGGKYCVGRRMKFKSCNTEP 480 CMKQKRDFREEQCAHFDGKHFNINGLLPSVRWFPKYSGIL 520 MKDRCKLFCRVAGNTAYYQLRDRVIDGTPCGQDTNDICVQ 560 GLCRQAGCDHILNSKVRKDKCGICGGDNSSCKIVAGIFNI 600 VHYGYNIVVRIPAGATSIDVRQHSFSGKSEDDNYLALSNS 640 KGEFLLNGDFVVSMSKREVRVGSAVIEYSGSDNVVERLNC 680 TDRIEEELLLQVLSVGKLYNPDVRYSFNIPIEDKPQQFYW 720 NSHGPWQACSKPCQGERRRKLVCTRESDQLTVSDQRCDRL 760 POPGPVTEACGIDCDLRWHVASKSECSAQCGLGYRILDIH 800 CAKYSRMDGKTEKVDDSFCSSQPRPSNQEKCSGECSTGGW 840 RYSAWIECSRSCDGGTQRRRAICVNIRNDVLDDS 874

Created: Saturday, April 10, 1999 11:40 AM

Fig. 8 (con't)

360	370	380	390	400	410	420
لسلسلسل	•					•
ACAGATGGAACCACA						
TGACCACAGGATGGT		_				
GCTTCTATCTATAAA	GACTCAAGTAT	MGGAAATTT	TTATAATTAA	GITATIGIGA	ACTTAGTTGT	SATTC 560
ATAATGAACAGGAAG						
GCACTCAAAGAACTA	CITICGGTGGGZ	ATTCAGCACG	ACACAGCCGI	ICIGGICACA	AGGGAAGATA'	icigo 700
710	720	730	740	750	760	770
لسلسلسلس						
AGAGCTCAGGACAAA'	IGIGACACCIT	PAGGICTIGC	TGAACTGGGA	ACCATTIGCG/	ACCCCTACCG	AAGCT 770
GTTCCATTAGTGAAG	ACAGIGGGCIC	BAGCACAGCT	TTCACAATAG	CICACGAGCIO	EGGCCATGIG	ritaa 840
TATGCCTCACGATGA	CAGCAATAAAT	rgcaaagaag	AAGGAGTTAA	GAGTCCCCAG	CATGTCATGG	CACCA 910
ACACTGAACTTCTAC	ACCAACCCCTC	GATGIGGIC	AAAGIGCAGI	CGGAAATACA	ICACIGAGITO	CTAG 980
ACACTGGGTACGGAG	AGIGCITGCIC	EAATGAACCT	GCATCCAGGA	CCTATCCTTTC	CCTTCCCAA(CTGCC 1050
1060	1070	1080	1090	1100	1110	1120
لسلسيلسل	بليستليبين	لتتبليين	لتسليب		ليسلسي	
CGCCTTCTCTACAA	CGIGAATAAAC	CAATGIGAAC	TGATTTTTGG	GCCAGGCTCT	CAAGIGIGCC	CTAT 1120
ATGATGCAGTGCAGA	CGGCICIGGI	CAATAATGI	GGATGGAGCA	CACAAAGGCT	CAGGACICA(CACA 1190
CCCCTCCCCAGATO	GAACCGAGTG	rgagcctigga	AAGCACTGCA	AGTTTGGATT.	rigigirece	AAAGA 1260
AATGGAGGCCCTGC	AATTGATGGA?	roctegegag	GITGGAGCCA	CITIGGGACC:	IGCICAAGAA	CGIGT 1330
GGAGGAGGCATCAAA	ACAGCCATCAC	CAGAGTGCAA	CAGACCAGAG	CCAAAAAATG	GIGGGAAGTA	CIGIG 1400
1410	1420	1430	1440	1450	1460	147 0
استلسلست	سسلس	سسلسه	لتسليب	لسلسل		
TAGGAAGGAGAATGA	AGITCAAATC	CTGCAACACG	GAGCCCTGCA'	TGAAGCAGAA	CGAGACTTO	CGAGA 1470
GGAGCAGIGICCICA	CTTTGATGGC	AAACACTTCA	ACATCAATGG	TCTCCTCCCC	AGCGTACGCT	3GTTT 1540
CCTAAGTACAGCGGA	ATTTTGATGAX	AGGACCGGTG	CAAGITGITC	TGCAGAGTGG	CAGGAAACAC	AGCCT 1610
ACTACCAGCTCCGAG	ACAGAGIGAT!	IGACGGAACC	CCTTGTGGCC	AGGACACAAA	IGACATCIGI	FICCA 1680
AGGCCTTTGCCGGCA	AGCIGGATGIC	SATCATATTT	TAAACTCAAA	GGTCCGGAAA(GATAAATGIG	GATT 1750
1760	1770	1780	1790	1800	1810	1820
البينيلينينا المتنابينا	لسيلسب	لتتبليت	<u> </u>	التستابيين	ليبينانين	
TGTGGTGGAGATAAT	TCTTCATGCAZ	AAACAGTGGC	AGGAACATTT	AACACTGTCC	ATTATEGTTA	CAATA 1820
CTGTTGTCCGAATTC				•		
GGATGACAACTACCT						
ATGTCCAAAAGGGAG						
GACTGAACTGTACGG						

Fig. 8 (con't)

2110	2120	2130	2140	2150	2160	2170
ساسساست	لتتبليتين	ببيابي	لتنسلتينا	لتسلست	لتشلست	ــــــــــــــــــــــــــــــــــــــ
CCCAGATGTGCGG	TACTCATTCAAT	ATTCCCATT	GAGGACAAACC	TCAGCAATTI	TACTGGAACA	GTCAC 2170
GGCCGTGGCAAG						
CTGATCAGCTAAC						
CCCCACAGACTGT	GACTIGAGGIGG	CACGITGCC	AGCAAGAGCGA	ATGCAGTGCC	CAGIGIGGII	TIGGGC 2380
TACCGTACTTTAG	ACATCCACTGTC	CCAAATACA	CAGGATGGAC	CGGAAGACGC	AGAAGGTGGA	ATGACA 2450
2460	2470	2480	2490	2500	2510	2520
		سيلسب	ليبيليين	لتبيلينين	لتتبليين	Luul -
GITICIGTAGCAG						
GCGCTATTCAGCC						
GTCAACACCCGCA						

Fig. 9A

10	20	30	40	50	60	70
TCACGCACGCCTTCC				-		
CCGCGTGGACCACAA			•			
GGGCCACAGCCGAGT						-
CCCACCTCCCCTCTA						
cccccccccccc						
360	370	380	390	400	410	420
CAGCACCTGTGGAGG	CIGCACGGO	CIGATOGIGG	CAGACGAGGA	AGAGTACCTG:	ATTGAGCCCC	IGCAC 420
GGTGGGCCCAAGGGT	ICICGGAGCO	COGAGGAAAG	TGGACCACAT	GIGGIGTACA	AGCGTTCCTC	ICIGC 490
GTCACCCCCACCTGG	ACACAGCCTG	TOGAGTGAGA	GATGAGAAAC	CGIGGAAAGC	3CCGCCATGG	IGGCT 560
GCGGACCTTGAAGCC	ACCGCCTGCC	AGACCCCTGG	GGAATGAAAC	AGAGCGTGGC	CAGCCAGGCC	IGAAG 630
CGATCGGTCAGCCGA	GAGCGCTACG	TGGAGACCCT	GGIGGIGGCT	GACAAGATGA'	IGGIGGCCTA'	ICACG 700
710	720	730	740	750	760	770
mulmulmul	لسيلس	لتسابين	لتتبليين	لتتبليين	لتسلسنا	<u>l</u>
GGCGCCGGGATGTGG	AGCAGTATGT	CCTCCCCATC	ATGAACATTG	TIGCCAAACT	TTTCCAGGAC	ICGAG 770
TCTGGGAAGCACCGT	PAACATOCTO	GIAACICGCC	TCATCCTGCT	CACGGAGGAC	CAGCCCACTC	IGGAG 840
ATCACCCACCATGCO	3GGAAGTCCC	TAGACAGCTT	CTGTAAGTGG	CAGAAATCCA	TOGTGAACCA	CAGCG 910
GCCATGGCAATGCCA	ITCCAGAGAA	COGIGIOGCI	AACCATGACA	CAGCAGIGCIV	CATCACACGC	TATGA 980
CATCIGCATCTACAA	GAACAAACCC	TGCGGCACAC	TAGGCCTGGC	CCGCIGGGCG	GAATGTGTGA	3CGCG 1050
1060	1070	1080	1090	1100	1110	1120
لسلسلسل	لتتبليب	لتسليب	لسيلس	لتسليب	ليسلسب	ــــــــــــــــــــــــــــــــــــــ
AGAGAAGCTGCAGCG	ICAATGAGGA	CATTGGCTGO	CACAAGCGIT	CACCATTGCC	ACGAGATCGC	GCACA 1120
CATTCGGCATGAACC	ATGACGGCGT	GGGAAACAGC	TGTGGGGCCC	GTGGTCAGGA	CCCAGCCAAG	TCAT 1190
GGCTGCCCACATTAC	CATGAAGACC	AACCCATTCG	TGTGGTCATO	CTGCAACCGT	GACTACATCA	CCAGC 1260
TTTCTAGACTCGGGO	CIGGGGCICI	GCCTGAACAA	ccesccccc	AGACAGGACT.	TIGIGIACCC	GACAG 1330
TGGCACCGGGCCAAG	CTACGATGC	AGATGAGCAA'	IGCCGCITIC	AGCATGGAGT	CAAATCGCGT	CAGTG 1400
1410	1420	1430	1440	1450	1460	1470
لستلسلسي	لتتبليين	لسيلسب	لتسلسنا	للتسليبيا	ليسلسيا	
TAAATACGGGGAGGT	CIGCAGCGAG	CIGIGGIGIC	TGAGCAAGAG	CAACCGGTGC	ATCACCAACA(CATC 1470
CCGGCCGCCGAGGGC	ACGCTGTGCC	AGACGCACAO	CATCGACAAG	GGGIGGIGCI	ACAAACGGGIY	CTGTG 1540
TCCCCTTTCCGTCCC	3CCCAGAGGG	TGTGGACGGA	GCCIGGGGGC	CGTGGACTCC	ATGGGGGGAC.	IGCAG 1610
CCGGACCTGTGGCGG	COCCEIGICC	TCTTCTAGTO	GTCACTGCGA	CAGCCCCAGG	CAACCATCG	3GGC 1680
AAGTACTGTCTGGGT	GAGAGAAGGO	GGCACCGCTO	CTGCAACACG	GATGACTGTC	CCCCIGGCIC	CCAGG 1750

Fig. 9A (con't)

1760	1770	1780	1790	1800	1810	1820
سيلسيليب	لتسلسيا	لببيليين	لتستليين	لسيلسي		
ACTICAGAGAAGIC	CAGIGITCIGA	ATTTGACAGO	ATCCCTTTCC	GIGGGAAATT	CTACAAGTGG	AAAAC 1820
GTACCGGGGAGGGC	GCGTGAAGGCC	IGCICGCICA	CGAGCCTAGC	GGAAGGCTTC	AACTICIACA(CGGAG 1890
AGGGCGGCAGCCGT	rggregacegea	CACCCIGCCG	TCCAGACACC	GIGGACATIT	GCGICAGIGG	CGAAT 1960
GCAAGCACGTGGGC	TIGOGACOGAGI	CIGGGCICC	GACCIGCGG	AGGACAAGTG	CCGAGIGIGI	35CGG 2030
TGACGGCAGTGCCT	rGCGAGACCATO	GAGGGGGTCI	TCAGCCCAGC	CICACCIGGG	GCCGGGIACG	AGGAT 2100
2110	2120	2130	2140	2150	2160	2170
سيلسلس	ليتبيلينين	لتتنايين	ليستليبي	لسلسب	لسسلسب	
GICGICTGGATTCC	CAAAGGCTCCG	ICCACATCII	CATCCAGGAT	CTGAACCICT	CTCTCAGTCA	CITGG 2170
CCCTGAAGGGAGAC	CAGGAGTCCCT	CIGCIGGAG	EGGCTGCCTC	XGGACCCCCCA	GCCCCACCGIV	CIGCC 2240
TCTAGCTGGGACC	ACCITICAACIG	CGACAGGGGC	CAGACCAGGI	CCAGAGCCTC	GAAGCCCTGG	GACCG 2310
ATTAATGCATCTC						
CCCCCATCGCCCG	IGACTOGCTGCC	CCCCTACTCC	TGGCACTATO	CCCCTCGAC	CAAGIGCICG	GCCCA 2450
2460	2470	2480	2490	2500	2510	2520
<u>ll</u>	لتتتليين	لتتبليين	لتتسليسيا	ليتبليينا	لسيطييي	
GIGIGCAGGCGGIZ						
CACTACTGCAGTG	CCACAGCAAGC	TGCCCAAAAC	CACCGCGCC	TIGCAACACGC	AGCCTTGCCC	TCCAG 2590
ACTGGGTTGTAGG	GAACTOGTOGCT	CIGCAGCCGC	CAGCTGCGATC	CAGGCGTGCC	CAGICGCICG	GICGI 2660
GIGCCAGCGCCGC	FICICIGCCGCG	GAGGAGAAGG	CGCTGGACG	ACAGCGCATGC	COGCAGCOGC	GCCCA 2730
CCTGTACTGGAGG	CCIGCCACGGCC	CCACTIGCCC	TCCGGAGTG	EGCAACCCTCC	ACIGGICIGA	GIGIA 2800
2810	2820	2830	2840	2850	2860	2870
<u></u>	لتبتيلينيا	ليسلسب	Liuliui	لتسليسا	لسبيليين	
CCCCAAGCTGTGG	CCTCCTCTCCC	CCACCGAGIC	GICCITIGIA	AAGAGTGCAGA	ATCAACGATĆT	ACTCT 2870
GCCCCTGGGCAC	TGCCTTCCTGCA	GCCAAGCCAC	CATCTACTA	rGCGATGTAAC	TTGCGCCGCT	GCCCT 2940
CCTCCCCCCTCCC	TGACCAGTGAGI	CCCCTCACTO	JITCCACACA(FIGIGGCCICC	SCCACCACCA	GCGCA 3010
CAGTGCGCTGCAC	CAGCCACACCGC	CCAGCCATC	TOGAGAGTGC	ACTGAAGCCTT	GCGGCCATCC	ACCAT 3080
GCAGCAGIGIGAG	GCCAAGIGIGAC	AGIGIGGIG	CCCCTCGAG	ATGGCCCAGA!	GAATGCAAGG	ATGTG 3150
3160	3170	3180	3190	3200	3210	3220
سلسلس	لتسليسنا	سيليب	سيبليين	ليتسلبينا	ليتبلينيا	
AACAAGGIGGCTT	ACTGCCCCCTGC	TIGCTCAAAT.	ITCAGITCIG	[AGCCGAGCC]	PACTICOGOCA	GATGT 3220
GCTGCAAAACCTG	CCAAGGCCGCta	gggtacctg	gaaccaacct	ggagcacaggo	ctgaggcaggg	gacat 3290
cccactggagagg	gcatgagggaaa	agggggctt	gaattgaagg	gtgagatgcag	gttgaaagtta	itttat 3360
tgggtaaccctac	agggeteetgad	taaggggtg	gagaagagct	ggctacccagg	gaccctctgo	tgtat 3430
cttgcccagttga	tagtgaagagag	gaggactcct	tgttgcacac	atatttaagto	cctagcacco	ectece 3500

Fig. 9A (con't)

				•					
	3510	3520	3530	3540	3550	3560	3570		
لمسلم	mulmut	<u> </u>	بلينيانيي	بليسلين	سيسليب	لتساسي	ــــــــــــــــــــــــــــــــــــــ		
accct	ttgatcggaal	catgtactgt	gaagagtgggg	gtggggaggg	gtgtgctgg	tgecetgece	cctac 3570		
			.ggggggattt						
			acgaaggggaa						
			ccatcatggt						
caccaagaagcettacattaaaaaagttgtgttateetacaaaaaaaaaa									
	3860	3870	3880	3890	3900	3910	3920		
<u> </u>									
ggtaco	ccaattogcgo	tatagtaaat	ngggtntta	3885					

26/54 Fig. 9B

human ADAM TS-\$10
10 20 30 40 4
SRTPSGLKMSSCPVWRAMRSPSPPAWITTGHCWPSRHLLP 40
GAAPRHOGHSRVPPLLQSGLASTHFLLNLTRSSRLLAGRV 80
SVEYWIREGLAWDRAARPHCLYAGHLOGQASSSHVAISIC 120
GGLHGLIVADEEEYLIEPLHGGPKGSRSPEESGPHVVYKR 160
SSLRHPHLDTACGVRDEKPWKGRPWWLRTLKPPPARPLGN 200
210 220 230 240 Mahre protesse
ETTEROODET KODET KODETNA KEITE LA KADIKAMA KANLICERDINKOO. 240
YVLAIMNIVAKLFQDSSLGSIVNILVIRLILLITEDQPTLE 280 SVSRERY
ITHHAGKSLDSFCKWQKSIVNHSGHGNAIPENGVANHDIA 320
VLITRYDICIYKNKPCGTLGLARWAECVSAREAAASMRTL 360
AATSVHICHEIGHIFGMNHDGVGNSCGARGQDPAKLMAAH 400
410 420 430 440
ITMKINPFVWSSCNRDYITSFLDSGLGLCLNNRPPRQDFV 440
YPTVAPGQAYDADEQCRFQHGVKSRQCKYGEVCSELWCLS 480
KSNRCITNSIPAAEGILCQIHTIDKGWCYKRVCVPFGSRP 520
EGVDGAWGPWTPWGDCSRTCGGGVSSSSRHCDSPRPTTGG 560
KYCLGERRRHRSCNIDDCPPGSQDFREVQCSEFDSIPFRG 600
610 620 630 640
KFYKWKTYRGGGVKACSLTSLAEGFNFYTERAAAVVDGTP 640
CRPDIVDICVSGECKHVGCDRVLGSDLREDKCRVCGGDGS 680
ACETIEGVFSPASPGAGYEDVVWIPKGSVHIFIQDLNLSL 720
SHLALKGDQESLLLEGLPGTPQPHRLPLAGTTFQLRQGPD 760
OVOSLEALGPINASLIVMVLARTELPALRYRFNAPIARDS 800
810 820 830 840
LPPYSWHYAFWIKCSAQCAGGSQVQAVECRNQLDSSAVAP 840
HYCSAHSKLPKRQRACNTEPCPPDWVVGWSLCSRSCDAG 880
VRSRSVVCQRRVSAAEEKALDDSACPQPRPPVLEACHGPT 920
CPPEWATLLWSECTPSCGPGLRHRVVLCKSADQRSTLPPG 960
HCLPAAKPPSIMRCNLRRCPPARWYTSEWGECSTQCGLGQ 1000

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Fig. 9B (con't)

1010 1020 1030 1040

QQRTVRCTSHTGQPSRECTEALRPSTMQQCFAKCDSVVPP 1040

GDGPEECKDVNKVAYCPLVLKFQFCSRAYFRQMCCKTCQG 1080
R 1081

Fig. 10A

partial dequence of mouse ADAM TS-10 10 20 30 40 (See figure)							
(See fig. a)							
10 20 30 40							
<u> </u>							
AGCAGCAGCTGTGGTGGAACACCCTGCCGCCCTGAC 40							
ACGGIGGACATTIGIGICAGCGGCGAGIGCAAGCATGIAG 80							
GCTGTGACAGGGTCCTGGGTTCTCGGAGAGGACAA 120							
ATGCCGTGTGTGGGGGTGATGCCAGTGCCTGTGAGACC 160							
ATTGAAGGIGICITTAGCCCAGCITTGCCAGGAACTGGGI 200							
210 220 230 240							
miliantiantiantiantiantiantiantiantiantiant							
ATGAGGACGTCGGATCCCCAAAGGCTCGGTCCACAT 240							
TTTCATCCAAGATCIGAACCIGICCCIGAGICACCIGGCC 280							
CTAAAGGGGACCAAGAGTCTCTGCTACTGGAGGGGCTAC 320							
CTGGGACCCCCAACCTVACCGCCTTCCCCTGGVTGGGAC 360							
CACATTTCATCTACGGCAGGGCCGGACCAGGCACAGAGC 400							
410 420 430 440							
<u> </u>							
CIGGAAGCCCIGGGACCCATIAATGCATCICICATCATCA 440							
TEGTECTECCCAGECAGAGTTCCCTCTCCACTACCG 480							
CTICAATGCACCCATTGCCCGGGATGCACTGCCTCCCTAC 520							
TCCTGGCACTATGCCCCCTGGACCAAATGCTCAGCCCAGT 560							
GIGCAGGCGGCAGGICCAAGIAGIGGAGIGCCGAAA 600							
610 620 630 640							
<u> </u>							
TCAGCTGGACAGCTCAGCAGTGGCCCCACACTACTGTAGT 640							
GGCCACAGTAAATTGCCCAAGAGGCAGCGTGCCTGCAACA 680							
CAGAACCATGTCCACCAGATTGGGTTGTAGGAAACTGGTC 720							
ACCCTGCAGCCGTAGCTGTGACGCTGTGTGCGTAGCCGC 760							
TCAGIGGIGIGCCAACGCCGGGIGICIGCIGCAGAGGAAA 800							
810 820 830 840							
manual control							
AAGCCTTAGACGACAGTGCCTGTCCACAGCCACGCCCACC 840							
TGTGCTGGAGGCCTGCCAATGTGCCCTCCTGAG 880							
TGGGCAACCCTCGACTGGTGTGCCCCAAGCTGTG 920							
GCCTCGTCTCCCCCACCGAGTCGTCCTTTGTAAGAGTCC 960							
AGATCAACGATCTACTCTGCCCCTGGCCACTGCCTTCCT 1000							

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Fig. 10A (con't)

1010 1020 1030	1040	
andred and a standard and a standard a stan		
GCAGCCAAGCCACCATCTACTATGCGATGTAACTTGC	CCC 1040	
GCTGCCCTCCTGCCCGCTGGGTGACCAGTGAGTGGGG	TGA 1080	
GIGITCCACACAGIGIGGCCTCGCCAGCAGCAGCAGC	ACA 1120	
GTCCGCTGCACCAGCCACCCAGCCATCTCGAG	AGT 1160	
GCACTGAAGCCTTGCGGCCATCCACCATGCAGCAGTG	TGA 1200	
1210 1220 1230	1240	
سلسبلسلسلسلسلسلسلس	11	
GCCCAAGTGTGACAGTGTGGTGCCCCCTGGAGATGGC	CCA 1240	
GAAGAATGCAAGGATGTGAACAAGGTGGCTTACTGCC	CCC 1280	
TGGIGCTCAAATTICAGITCTGTAGCCGAGCCTACTT	CCG 1320	
CCAGATGTGCTGCAAAACCTGCCAAGGCCGCTAGGGTZ	ACC 1360	
TGGAACCAACCTGGAGCACAGGCTGAGGCAGGGGACA	TCC 1400	
1410 1420 1430	1440	
		
CACTOGAGAGGCATGAGGGAAAGGGGGCTTGAATT	GAA 1440	
GGGIGAGATGCAAGTTGAAAGTATTTATTTGGGTAAC	CCC 1480	
TACAGGCTTCTGACTTAAGGGGTGGAGAANAGCTGG	CTA 1520	
CCCCAGGGACCCTTTTGTTGGATCTTGGCCCANTTGA	TAG 1560	
TGAAGAGAGAGCTTCTTGGTGVACACATTTTTAAG	TCC 1600	
1610 1620 1630	1640	
	111	
TTAGACCCTTCCACCNTTGATCGGATATGTCTGGGAAG	GAG 1640	
QN 1642	• •	

30/54

Fig. 10B

10)	20	30	4 0	monse	ADAM TSIO	
لبييلييي		بستنسب	لبييليي	للس			
AAAVVDGTPC	RPDIVDI	CVSGECKHV	GCDRVLGSDI	REDK 4	0		
CRVCGGDGSA	CETIEGV	FSPALPGIC	YEDVWIPKO	SVHI 8	0		
FIQDLNLSLS	HLALKGD	QESLLLEGI	PGTPQPXRLE	LXGT 1	20	•	
TFHLRQGPDQ							
FNAPIARDAL	PPYSWHY.	APWIKCSAC	CAGGSQVQV	JECRN 2	00		
21	0	220	230	240			
لتستليسا	سلسب	ىلىسىلىر	لسلسل	حلبب			
QLDSSAVAPH	YCSGHSK	LPKRQRACI	TEPCPPDWV	700NWS 2	40		
RCSRSCDAGV	RSRSVVO	QRRVSAAEE	KALDDSACP	OPRPP 2	80	•	
VLEACQGPMC	PPEWATL	DWSECTPSC	GPGLRHRVVI	CKSA 3	20		2
DORSTLPPGH	CLPAAKP	PSIMRCNLE	RCPPARWTS	SEWGE 3	60		
CSIQCGLGQQ	QRTVRCT	SHTGQPSRE	CTEALRPSIN	100CE 4	.00	•	
41	0	420	430	44 0			
لسيلسي	بالبيد	بليبيلي	للسللين			 	 .
AKCDSVVPPG	DGPEECK	DVNKVAYCE	PLVLKFQFCSI	RAYFR 4	.40		
QMCCKTCQGR	450						

Fig. 11A

Ligated 459225+482392 with Sac I(168)&Eco RI(or Not I) Cloning site:5';Eco RI 3';Not I Vector; PI7T3 pac.

You can put this construct to pcDNA3.1(+) for transfection 5'-UTR is 50bp &3'-UTR is 175bp

210-215; in 482392 it's TCCTAC(SY).

			•		
10	20	30	40		
	بلبييلب	بلتستليب			
gaattcggcacgaggca	gtgtccgatt	ctgattccg	gcaa 40		
ggatccaagcATGGAATG	3010000100	XGGCAACTCC	TGGC 80		
ACACIGCICCICITICIO	CTTTCCTC	CICCIGAGI	TCCA 120		
GGACCGCACgctCCGAG	GAGGACCGGC	ACGCCTAT	33GA 160		
TGCCTGGGGCCCCATGGA	FIGAATGCTC	ACGCACCIG	CGGG 200		
210	220	230	240		
	بالبيبات	عليتبلين	ш		
GGTGGGGCCCCAACTC	ICIGAGGCGC	TGCCTGAGC	AGCA 240		
AGAGCTGTGAAGGAAGA	AATATCCGAT	ACAGAACAT	GCAG 280		
TAATGTGGACTGCCCAC	CAGAAGCAGG	TGATTTCCG	AGCT 320		
CAGCAATGCTCAGCTCAG	IAATGATGIC	'AAGCACCAT	360 360		
AGITTTATGAATGGCTTC	CIGIGICIA	ATGACCCTG	ACAA 400		
410	420	430	440		
mulmulmulm	بالتبيلي	بليسلين	<u>l</u>	·····	
CCCATGTTCACTCAAGTC	CCAAGCCAA	AGGAACAAC	CTG 440		
GTTGTTGAACTAGCACC	PAAGGICTTA	GATOGTACO	CGTT 480		
GCTATACAGAATCTTTG	GATATGTGCA	TCAGIGGIT.	EATG 520	•	
CCAAATTGTTGGCTGCG	ATCACCAGCT	GGGAAGCAC	CGTC 560		
AAGGAAGATAACTGTGG	GICIGCAAC	GAGATOGG:	ICCA 600		•
610	620	630	640		
<u> سىلىسلىسلى</u>	بالتبيات	بليتيلي	ш		
CCTGCCGGCTGGTCCGAC	OGCAGTATA	AATCCCAGC:	ICIC 640	•	•
CGCAACCAAATCGGATGA	YTACTGTGGI	TGCAATTCC	TAT 680		
GGAAGTAGACATATTCG	CTTGTCTTA	AAAGGICCIC	GATC 720		
ACTTATATCTGGAAACC	AAAACCCTCC	'AGGGGACTAI	AAGG 760		
TGAAAACAGTCTCAGCTC	CACAGGAAC	TTTCCTTGTC	3GAC 800		

and the state of the state of

32/54 Fig. 11A (con't)

810 820 830 840
AATTCTAGTGTGGACTTCCAGAAATTTCCAGACAAGAGA 840
TACTGAGAATGGCTGGACCACTCACAGCAGATTTCATTGT 880
CAAGATTOGTAACTOGGCTCCGCTGACAGTACAGTCCAG 920
TICATCITCTATCAACCCATCATCCACCGATGGAGGGAGA 960
CGGATTTCTTCCTTGCTCAGCAACCTGTGGAGGAGGTTA 1000
1010 1020 1030 1040
TCAGCTGACATCGCCTGAGGATCTGAGGAGCAAC 1040
CGIGIGGITGCIGACCAATACIGICACTATIACCCAGAGA 1080
ACATCAAACCCAAGCTTCAGGAGTGCAACTTGGA 1120
TCCTTGTCCAGCCAGTGACGGATACAAGCAGATCATGCCT 1160
TATGACCTCTACCATCCCCTTCCTCGGTGGGAGGCCACCC 1200
1210 1220 1230 1240
CATGGACCGCGTGCTCCTCGTGTGCGGGGGGCCATCCA 1240
GAGCCGGCAGTTTCCTGTGTGGAGGACATCCAGGGG 1280
CATGICACTICAGIGGAAGIGGAAATGCATGTACACCC 1320
CTAAGATGCCCATCGCGCAGCCTGCAACATTTTTGACTG 1360
CCCTAAATGGCTGGCACAGGGCTCCCGTGCACAGTG 1400
ACGTGTGGCCAGGCCTCAGATACCGTGTGGTCCTCTGCA 1440
TOGACCATOGAGGAATGCACACACGAGGCTGTAGCCCAAA 1480
AACAAAGCCCCACATAAAAGAGGAATGCATCGTACCCACT 1520
CCCTGCTATAAACCCAAAGAGAAACTTCCAGTCGAGGCCA 1560
AGTIGCCATGGITCAAACAAGCICAAGAGCTAGAAGAAGG 1600
1610 1620 1630 1640
ACCTCCTCTCTCAGACGAGCCCTCCTAAgttgtaaaagca 1640
cagactgttctatatttgaaacttttgtttaaagaaagca 1680
gtgtctcactggttgtagctttcatgggttctgaactaag 1720
tgtaatcatctcaccaaagctttttggctctcaaattaaa 1760
gattgattagtttcaaaaaaaaaaaaaaaaaagatgcggc 1800

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PCT/US00/21223

33/54

g. 11A (con't)

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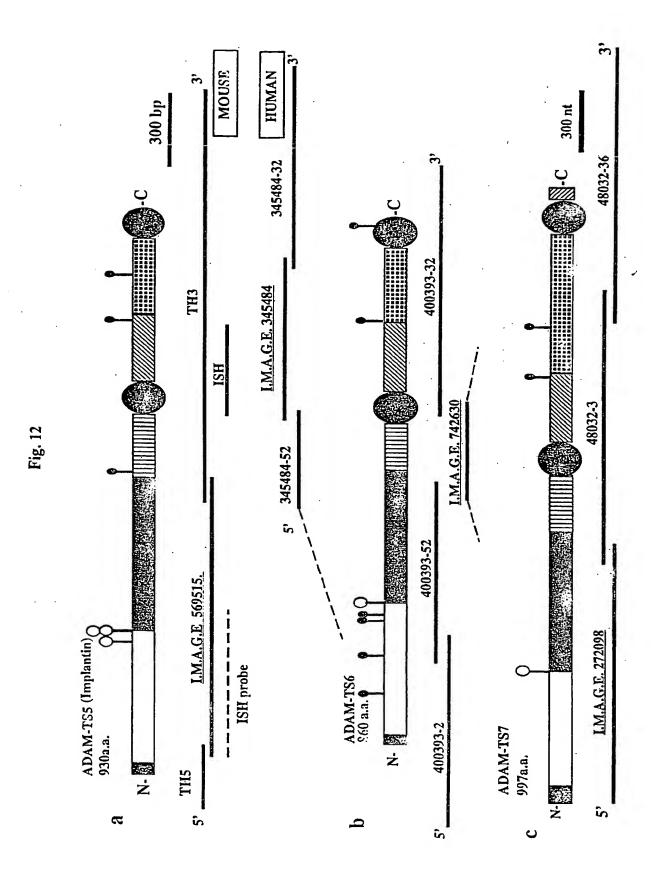
34/54 Fig. 11B

Created: Wednesday, May 5, 1999 10:19 AM

Ligated 459225+482392 with Sac I(168)&Eco RI(or Not I) Cloning site:5';Eco RI 3';Not I Vector; PI7T3 pac.

human ADAM-TSRI Adam-Ts related protein -1.

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10 20 30			
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MECCREATEGILLLFLAFILLSSRTARSEE		5 Signal po	ephde
PWSECSRTCGGGAANSLRRCLSSKSCEGRN	TIRYRTCSNVD 8	30	
CPPEAGDFRAQQCSAHNDVKHHGQFYEWLF	VSNDPDNPCS 1	120	
LKCOAKGITLVVELAPKVLDGIRCYTESLI			
GCDHQLGSTVKEDNCGVCNGDGSTCRLVRG			
210 220 23	30 240		
ليتبيلين أيساليساليساليسا			
SDDIVVAIPYGSRHIRLVLKGPDHLYLEIK		240	
LSSTGTFLVDNSSVDFQKFPDKEILRMAGE	· -		
		220	
NSGSADSIVQFIFYQPIIHRWREIDFFPCS		/ : ` ` ` / / / / / / / / / / / / / / / / / / / / / / / / / /	KPKLQE
SAECYDLRSNRVVADQYCHYYPENIKPKPK			
ASDGYKQIMPYDLYHPLPRWEATPWIACSS	SCCGCGIQSRA 4	400	
410 420 43	30 440		
ليتبايينيانينيانييانين	لسسسل		
VSCVEEDIQGHVTSVEEWKCMYTPKMPIAQ		440 (C) QELEEGAAV	
LAQEWSPCIVICGQGLRYRVVLCIDHRGM		480	
HIKEECIVPTPCYKPKEKLPVEAKLPWFKQ	DAQELEEGAAV !	520 C- terminal gs	
SEEPS. 526		1 . 10040	the
Similar to ADA	M-TS fai	my but have	
Similar 16		1 - 1 - 1011	One
1 11 and cleared as	nd disc	itegren acomes.	, 4
prometaupura	1. 1. 1.0	he a inhibitor	4 1~
humpheris is that	this ma	~	
prometalloprolease as hypothesis is that			
formly			
V			



a	
MRLEWASILLILILISASCISIAADSPAAAPAQDKTRQPQAAAAAAEPDQPQCEETRERGHIQPLAGQRRSGGLVHNIDQ	80
LYSGGGKVGYLVYAGGRRFLLDLERDDIVGAAGSIVTAGGGLSASSGHRGHCFYRGIVDGSPRSLAVFDLCGGLDGFFAV	160
KHARYTLKPLLRGSWAEYERIYGDGSSRILHVYNREGFSFEALPPRASCETPASPSGPQESPSVHSRSRRRSALAPQLLD	240
######################################	320
LIDKDISLEVSKNAATILKNFČKWQHQHVQLGDDHEEHYDAAILFTREDLÖGHHSCDILGMADVGITČSPERSČAVIEDD	400
GLHAAFTVAHEIGHILGISHDSKFCEENFGTTEDKRIMSSILTSIDASKPWSKCTSATTTEFLDOGHGVCILDLPRKQIGHILGISHDSKFCEETFGSTEDKRIMSSILTSIDASKPWSKCTSATTTEFLDOGHGVCILDLPRKQI	480
LGPEELPGQTYDATQQCNLTFGPEYSVCPGMDVCARLWCAVVRQQQMVCLTKKLPAVEGTPCGKGRVCLQGKCVDKTKKK LGPEELPGQTYDATQQCNLTFGPEYSVCPGXDVCARLWCAVVRQQQMVCLTKKLPAVEGTPCGKGRICLQGKCVDKTKKK	560
YYSTSSHGMGSWGFWGQCSRSCGGGVQFAYRHCNNPAPRNSGRYCTGKRAIYRSCSVTPCPPNGKSFRHEQCEAKNGYQ YYSTSSHGMGSWGSWGCSRSCGGGVQFAYRHCNNPAPRNVGRYCTGKRAIYHSCSIMPCPPNGKSFRHEQCEAKNGYQ	640
SDAKGVKTFVEWVPKYAGVLPADVCKLTCRAKGTGYYVVFSPKVTDGTECRPYSNSVCVRGRCVRTGCDGIIGSKLQYDK SDAKGVKTFVEWVPKYAGVLPADVCKLTCRAKGTGYYVVFSPKVTDGTECRPYSNSVCVRGKCVRTGCDGIIGSKLQYDK	720
* *	800
INGTVMNYSGWSHRDDFLHGMGYSATKEILIVQILATDPTKALGVRYSFFVPKKTTQKVNSVISHGSNKVGPHSTQLQWV INGTVMNYSGWSHRDDFLHGMGYSATKEILIVQILATDPTKPLDVRYSFFVPKKSTPKVNSVTSHGSNKVGSHTSQPQMV	880
TGPWLACSRTCDIGWHTRTVQQQDGNRKLAKGCLLSQRPSAFKQCLLKKC TGPWLACSRTCDIGWHTRTVQQQDGNRKLAKGCPLSQRPSAFKQCLLKKC	930

Fig. 13

Hurskainen et al[^]. Fig. 2a

A CONTRACTOR

METIMKTLTWILSLIMASSEFHSDHRLSYSSQEEFLTYLEHYQLTTPIRVDQXGAFLSFTVKNEKHSRRRRSMDPIDPQQ 80

AVSKLFFKLSAYGKHFHLNLTTMTDFVSKHFTVEYWGKDGPQWKHDFLLNCHYTGYLQDQRSTTKVALSNCVGLHGVTAT 160

EDEEYFTEPLKNTTEDSKHFSYENGHPHVTYKKSALQQRHLYDHSHCGVSDFTRSGKPWMINDTSTVSYSLPINWTHIHH 240

RQKRSVSTERFVETLVVADKMAVGYHERKDIEHYTLSVMNIVAKLYRDSSLGWVNITVARLIVLTEDQPALEINHADK 320

SLDSFCKWQKSILSHQSDGVTTPENGIAHHDNAVLTTRYDICTYKNKPCGTLGLASVAGNCEPERSCSINEDIGLGSAFT 400

LAHETVHNFGMHDEIGNSCGRKVMKQQNYGSSHYCEYQSFFLVCLQSRLHHQLFREVCRELWCLSKSNRCVTNSIPAAE 480

GTLCQTGNIEKGWCYQGDCVPFGTWFQSIDGGWGFWSLWEDCSRTCGGGGVSSSLRHCDSPAPSGGGKYCLGERKRYRSCN 560

TDPCPLGSRDFREKQCADFDNMPFRCKYYNWKPYTGGGVKPCALWCLABGYNFYTERAPAVIDGTQCNADSLDICTNGEC 640

KHVGCINILGSDAREDRCRVCGGGGSTCDALEGFFNDSLPRGGYMEVVQIPRGSVHTEVREVAMSKNYTALKSECDDYYT 720

NGAWNTLWPRKFDVAGTAFHYKRPTDEPESLEALGPTSENLIVMVLLQEQNLGIRYKFNVPITRIGSGDNEVGFTWNHQP 800

WSECSATCAGGKMPTRQPTQRARWRIKHILSYALCLLKKLIGNISCRFASSCNLAKETLL 860

MFGGPSPRSPAPILRPLLLLICALAPGAPGPAPGRATEGRAALDIVHPVRVDAGGSFLSYELWPRALRKRDVSVRRDAPA 80

FYELQYRGRELRFNLTANQHLLAPGFVSETRRRGGLGRAHIRAHTPACHILGEVQDPELEGGLAAISACDGLKGVFQLSN 160

EDYFIEPLDSAPARRCHAQPHWYKRQAPERLAQRGDSSAPSTCGVQVVPELESRRERWEDRQQWRRPRIRRLHQRSVSK 240

EKWWETLWVADAKWWEYHCQPQVESYVLTIMMWAGLFHDPSIGNPIHITTURIVLLEDEEEDLKLTHHADWILKSFCKW 320

QKSILMKGDAHPLHHDTAILLITRKDLCAAMMRRCETLGLSHVAGMCQPHRSCSINEDIGLPLAFTVAHELGHSEGIQHIG 400

SCANDCEPVGKRPFIMPQLLYDAAPLIWSRCSRQYITRFLDRGWGLCLDDPPAKDIIDFPSVPRGVLYDVSHQCRLQYGA 480

YSAFCEDMINVCHILWCSVGTTCHSKLDAAVDGTRGGENKWCLSGECVPVGFRPEAVDGCWSGWSAWSICSRSGGMYOS 560

AERQCTOPTFKYKGRYCVGERKRFRLCNLQACPAGRPSFRHVQCSHFDAMLYKGQLHTWWPVMDVNFCELHCRPANEYF 640

AKKLRDAWDGTFCYQVRASRDLCINGICKNVGCDFEIDSGAMEDRCGVCHAGSTCHIVSGTFEEAEELGYVDVGLIPA 720

GAREIRIQEVAFAANFLALRSEDPEKYFLNGGWTQWIGDYQVAGTTFTYARRGWENLTSPGPTKEFWWIQVPASRGPG 800

GGSRGGVPRPSTTHGRSRPGGVSFGSVTEPGSEPGPPAAASTSVSPSLKWPNLWAAVHROGWQAPLGLCGWRRHIVING 880

PRLPTQLLFQESNRGVHYEYTIHREAGGHDEVPPPVFSWHYGFWIKCTVTCCRGEKWGRHSPTCRGLVSGGHWLQLPAH 960

CWATTGLEVCFSEPQFSICEMRIAIALCPRPACRVHG 997

Fig. 13 (con't)

		adamalysin II atrolysin A	HELGHNLGME HD HELGHNLGMV HD
		hADAM-9 hADAM-10 hADAM-15 hADAM-17 mADAM-19	HELGHNLGMNHD HEVGHNFGSPHD HELGHSLGLDHD HELGHNFGAEHD HEIGHNFGMSHD
	a	mADAM-TS1 hADAM-TS2 hADAM-TS3 hADAM-TS4 mADAM-TS5 hADAM-TS6 hADAM-TS7	HELGHVFNMP HD HETGHVLGME HD HETGHVLGME HD HELGHVFNML HD HEIGHL LG LS HD HEIVHN FGMNHD HELGH S FG I Q HD
	mADAM-TS1 hADAM-TS2 hADAM-TS3 hADAM-TS4 hADAM-TS5 hADAM-TS6 hADAM-TS7	W G P W G F W G A W S F W G P W G S W G S W G S W G S W G S W G S W G S W G S W G P W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G W S G	W G D C S R T C G G G V Q Y 20 F G S C S R T C G T G V K F 20 F G S C S R T C G T G V K F 20 W G D C S R T C G G G V Q F 20 W G Q C S R S C G G G V Q F 20 W G E C S R T C G G G V S S 20 W S I C S R S C G M G V Q S 20
b	mADAM-TS1 hADAM-TS2 hADAM-TS3 hADAM-TS4 hADAM-TS5 hADAM-TS6 hADAM-TS7	T M R E C I R T R Q C I R T R Q C I S S R D C A Y R H C I S L R H C I A E R Q C	N P H P A N G G R T C S G L 4 N P H P A N G G R T C S G L 4 R P V P R N G G K Y C E G R 4 N P A P R N N G R Y C T G K 4 S P A P S G G G K Y C L G E 4
	mADAM-TS1 hADAM-TS2 hADAM-TS3 hADAM-TS4 hADAM-TS5 hADAM-TS6 hADAM-TS7	R V R Y R A Y D F Q A Y D F Q R T R F R R A I Y H R K R Y R	C S R O D C 5 C N T E D C 5 C S L M P C 5 C N T D P C 5

Fig. 13 (con't)

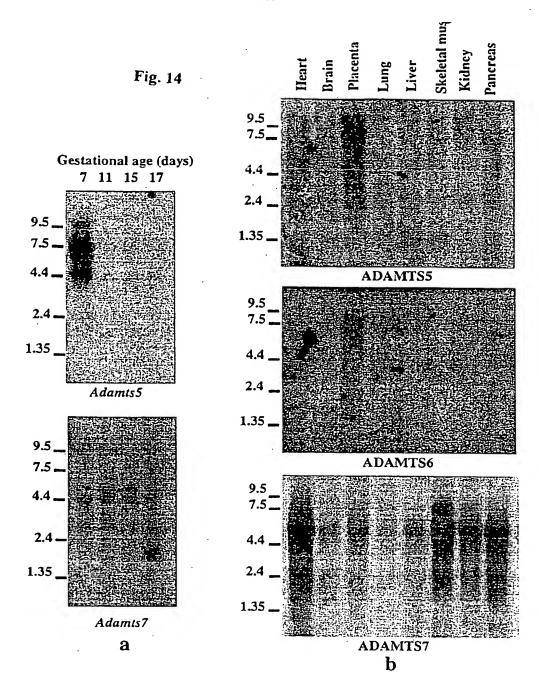


Fig. 15

ADAM-TS RELATED PROTEIN-1 (ADAM-TSR1)

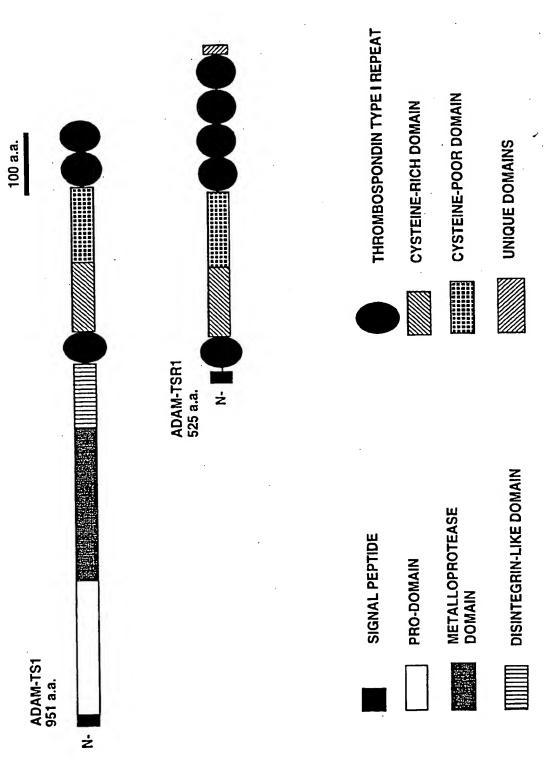


Fig. 15 (con't)

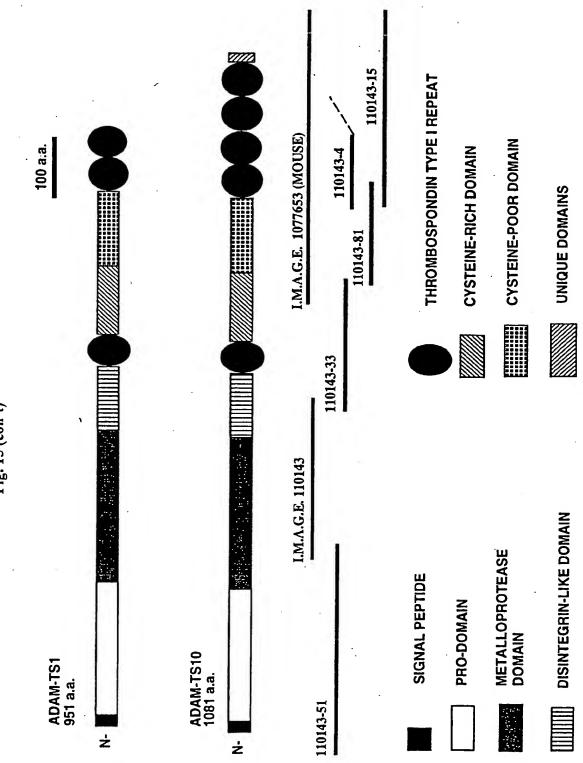


FIGURE 16 Pa

MSSCPWWRAMRSPSPPAWITIGHCWPSRHLLP 40 GAAPRHGGHSRVPPLLOSGLASTHFLLNLTRSSRLLAGRV 80 SVEYWTREGLAWQRAARPHCLYAGHLQGQASSSHVAISTC 120 GGLHGLIVADEEEYLIEPLHGGPKGSRSPEESGPHVVYKR 160 SSLRHPHLDTACGVRDEKPWKGRPWWLRTLKPPPARPLGN 200 ETERGOPGLKRSVSRERYVETLVVADKMMVAYHGRRDVEQ 240 YVLAIMNIVAKLFODSSLGSTVNILVIRLILLTEDQPILE 280 ITHHAGKSLDSFCKWQKSIVNHSGHGNAIPENGVANHDTA 320 VLITRYDICIYKNKPCGILGLARWAECVSAREAAASMRTL 360 AATSVHICHEIGHTFGMNHDGVGNSCGARGODPAKLMAAH 400 ITMKTNPFVWSSCNRDYITSFLDSGLGLCLNNRPPRODFV 440 YPTVAPGOAYDADEOCRFOHGVKSROCKYGEVCSELWCLS 480 KSNRCITNSIPAAEGILCOIHIIDKGWCYKRVCVPFGSRP 520 EGVDGAMGPWIPWGDCSRTCGGGVSSSSRHCDSPRPTIGG 560 KYCLGERRRHRSCNIDDCPPGSODFREVQCSEFDSIPFRG 600 KFYKWKTYRGGGVKACSLTSLAEGFNFYTERAAAVVDGTP 640 CRPDIVDICVSGECKHVGCDRVLGSDLREDKCRVCGGDGS 680 ACETIEGVFSPASPGAGYEDVVWIPKGSVHIFIQDLNLSL 720 SHLALKGDOESLLLEGLPGTPOPHRLPLAGTTFOLROGPD 760 OVOSLEALGPINASLIVMVLARTELPALRYRFNAPIARDS 800 LPPYSWHYAPWIKCSAOCAGGSOVQAVECRNQLDSSAVAP 840 HYCSAHSKLPKRORACNTEPCPPDWVGNWSLCSRSCDAG 880 VRSRSVVCQRRVSAAEEKALDDSACPOPRPPVLEACHGPT 920 CPPEWAALDWSECTPSCGPGLRHRVVLCKSADHRATLPPA 960 HCSPAAKPPATMRCNLRRCPPARWAGEWGECSAQCGVGQ 1000 RORSVRCTSHIGOASHECTEALRPPITOOCEAKCDSPTPG 1040 DGPEECKDVNKVAYCPLVLKFOFCSRAYFROMCCKTCOGH 1080 Created: Thursday, October 01, 1998 11:05 PM

•	10	20	30	40
بلبيب	سسلس	لسياسيا	لتستلسيا	
tcacgo	acgccttc	cggtctcaag/	ATGAGTTCCTG	TCCAG 40
		AGATCGCCTTC		
CACAAO	GGGGCACT	ECTEGCCTTC:	regecacetee	TCCCC 120
GGAGCA	GCGCCGCG	ECACGGGGGC	CACAGCCGAGI	CCCGC 160
CICITO	TACAAAGT	GCCTCGCCA(CACCCACTIC	CIGCT 200

FIGURE	16 (continu		Pa		
·					
210	220	230	240	·	
GAACCTGACCCGCAG	CTCCCGTCTA	ACTGGCAGGGC	CGCGTC 240		
TCCGTGGAGTACTGG	ACACGGGAG	CCTCCCTC	GCAGA 280		
GGGCGGCCCCC	ACTGCCTCTA	ACGCIGGICA(CTGCA 320		
GGGCCAGCCAGCAG	CTCCCATGIC	GCCATCAGC	ACCIGT 360		
GGAGGCCTGCACGGC	CIGATOGIC	CAGACGAGG?	AGAGT 400		
41 0	420	4 30	440		
البيطينيطينيا	 	سيلسيا	السلك		···
ACCIGATIGAGCCCC	TGCACGGTGC	EGCCCAAGGG!	TICTCG 440		,
GAGCCCGGAGGAAAG	IGGACCACAI	GIGGIGIAC	AGCGT 480		
TCCTCTCTGCGTCAC		- ·			
TGAGAGATGAGAAAO	/				
GCGGACCITGAAGCC	ACCGCCTGCC	CAGACCCCTGC	SGGAAT 600		
610	620 	630 Lagadaga	640		· .
GAAACAGAGCGIGGC	CAGCCAGGC	TIGAAGCGAT	CGTCA 640		
GCCGAGAGCGCTACG	TGGAGACCC	regregreec.	IGACAA 680		
GATGATGGTGGCCTA	TCACGGGGCG	CCCCGATGTCC	SAGCAG 720		
TATGTCCTGGCCATC	ATGAACATT	FITGCCAAAC.	TTTCC 760		
AGGACTCGAGTCTCG	GAAGCACCG.	TAACATCCT	CGTAAC 800		
810	820	830	840		•
	بيطييي	سيلسب	Luul	•	
TOGOCTCATCCTGCT	CACGGAGGA	CAGCCCACIC	CTGGAG 840	•	
ATCACCCACCATGCC					
AGTGGCAGAAATCCA					
TGCCATTCCAGAGAA		•	•		
GIGCICATCACACGC	TATGACATC	IGCATCTACA/	AGAACA 1000		
1010	1020	1030			
		•			
AACCCTGCGGCACAC					
TGTGAGCGCGAGAGA					
GCTGCCACAAGCGTT					
CATTCGGCATGAACC GGCCCGIGGICAGGA					
CCCCGIGGICAGGA	CCARCCARL	2CICAIGGCI(JULIAN 1200		

FIGURE 16 (continued)	Pa		
1210 1220 1230 1240			
ATTACCATGAAGACCAACCCATTCGTGTGGTCATCCTGCA 1240			
ACCGIGACTACATCACCAGCITTCTAGACTCGGGCCTGGG 1280			
GCTCTGCCTGAACAACCGGCCCCCCAGACAGGACTTTGTG 1320			
TACCCGACAGTGGCACCGGCCAAGCCTACGATGCAGATG 1360			
AGCAATGCCGCTTTCAGCATGGAGTCAAATCGCGTCAGTG 1400			
1410 1420 1430 1440			
<u> </u>			
TAAATACGGGGGGGCTCTGCGGGCTGTGTGTGTGTGAGC 1440	,		
AAGAGCAACCGGTGCATCACCAACAGCATCCCGGCCGCCG 1480	· ·		
AGGCACGCTGTGCCAGACGCACACCATCGACAAGGGGTG 1520	•		
GIGCTACAAACGGGICIGIGICCCCTTTGGGICGCGCCCA 1560			
GAGGTGTGGACGGAGCCTGGGGCCGTGGACTCCATGGG 1600			
1610 1620 1630 1640			
and make the standard of the s			
GCGACTGCAGCCGGACCTGTGCCGGCGGGGGTGTCCTCTTC 1640			
TAGTOGTCACTGCGACAGCCCCAGGCCAACCATCGGGGGC 1680			
AAGTACTGTCTGGGTGAGAGAGGCGCCACCGCTCCTGCA 1720			
ACACGGATGACTGTCCCCCTGGCTCCCAGGACTTCAGAGA 1760			
AGIGCAGIGITCIGAATTIGACAGCATCCCITTCCGIGGG 1800			
1810 1820 1830 1840			
AAATTCTACAAGTGGAAAACGTACCGGGGGGGGGGGGGG			
AGGCCIGCTCGCTCACGAGCCTAGCCGAAGGCTTCAACTT 1880			
CTACACGGAGAGGCGCAGCCGTGGTGGACGGGACACCC 1920	·		
TGCCGTCCAGACACGGTCGACATTTGCGTCAGTCGCGAAT 1960	.*		
GCAAGCACGIGGGCIGGACCGACCICGGCCICCGACCT 2000			
2010 2020 2030 2040			
GCGGAGGACAAGTGCCGAGTGTGTGGCGGTGACGCAGT 2040			
GCCTGCGAGACCATCGAGGCGTCTTCAGCCCAGCCTCAC 2080			
CTGGGGCCGGGTACGAGGATGTCGTCTGGATTCCCAAAGG 2120			
CICCGICCACATCITCATCCAGGATCTGAACCICICICC 2160			

AGICACTIGGCCCIGAAGGGAGACCAGGAGTCCCTGCTGC 2200

2210 2220 2230 2240
TGGAGGGCTGCCTGGGACCCCCAGCCCCACCGTCTGCC 2240
TCTAGCTGGGACCACCTTTCAACTGCGACAGGGGCCAGAC 2280
CAGGTCCAGAGCCTCGGACCGATTAATGCAT 2320
CICICATCGICATGGIGCTGCCCGGACCGAGCTGCCTGC 2360
CCTCCGCTACCGCTTCAATGCCCCCATCGCCCGTGACTCG 2400
2410 2420 2430 2440
and pulling the state of the st
CTGCCCCCTACTCCTGGCACTATGCGCCCTGGACCAAGT 2440
GCTCGGCCCAGTGTGCAGGCGGTAGCCAGGTGCAGGCGGT 2480
GGAGTGCCGCAACCAGCTGGACAGCTCCGCGGTCGCCCCC 2520
CACTACTGCAGTGCCCACAGCTGCCCAAAAGGCAGC 2560
GCGCCTGCAACACGGAGCCTTGCCCTCCAGACTGGGTTGT 2600
2610 2620 2630 2640
AGGGAACTGGTCGCTCTGCAGCCGCAGCTGCGATGCAGGC 2640
GIGCGCAGICGCICGIGIGCCAGCGCCGCGICICIG 2680
CCGCGGAGGAGGACGCCACGCCATGCCCGCA 2720
GCCGCGCCACCIGIACIGGAGGCCIGCCACGGCCCCACT 2760
TGCCCTCCGGAGTGGCCCTCGACTGGTCTGAGTGCA 2800
2810 2820 2830 2840
<u>inchendententententententen</u>
CCCCCAGCIGCGGCCCCCCCCCCCCCCCCCCCCCCCCCC
TTGCAAGAGCGCACGCGCCACGCTGCCCCCGGCG 2880
CACTGCTCACCGCCCAAGCCACCGCCACCATGCGCT 2920
GCAACTTGCGCCGCCCCCCGCCCGCTGGGTGGCTGG 2960
CGAGTGGGGTGAGTGCTCTGCACAGTGCGGCGGCAG 3000
3010 3020 3030 3040
CGCAGCGCTCGGTGCGCCACCACCGCCCAGG 3040
CGTCGCACGAGGCCCTGCGGCCGCCCACCAC 3080
GCAGCAGTGTGAGGCCAAGTGCGACAGCCCCAACCCCCGGG 3120
GACGCCCTGAAGAGTGCAACGATGTGAACAAGGTCGCCT 3160
ACTGCCCCTGGTGCTCAAATTTCAGTTCTGCAGCCGAGC 3200

FIGURE 1	6 (continue	d) 										
	3220	3230	3240									
	ىبلىسىنى	سلسسلت										
CTACTTCCGCCAGATGTC	CTCCAAAAC	CTGCCAGGGC	CAC 3240)								
taggggggggggggac	ccggagccac	agctggcggg	gtc 3280)	_							
tecgeegecagecetge				_								
cggggggggggaactgg				_								
ggaagttatttattggg				_								
3410	3420	3430	3440									
	بيلتنيلن	سلسيان	ليب			·· · · · · · · · · · · · · · · · · · ·						
aggregations 3409	•	•				,						

FIGURE 17

Molecular Weight 216301.30 Daltons

- 1934 Amino Acids
- 234 Strongly Basic(+) Amino Acids (K,R)
- 216 Strongly Acidic(-) Amino Acids (D,E)
- 477 Hydrophobic Amino Acids (A, I, L, F, W, V)
- 657 Polar Amino Acids (N,C,Q,S,T,Y)

7.734 Isolectric Point

24.102 Charge at PH 7.0

MQFVSWATLLTLLVRDLAFMGSPDAAAAVRKDRLHPRQVKLLETLSEYEIVSPIRVNALG	60
EPFPINVHFKRTRRSINSATDPWPAFASSSSSSTSPQAHYRLSAFGQQFLFNLTANAGFI	120
APLFTVTLLGTPGVNQTKFYSEEFAELKHCFYKGYVNTNSEHTAVISLCSCMLGTFRSHD	
GGYFIEPLQSMDEQEDEEEQNKPHIIYRRSAPQREPSIGRHACDISEHKNRHSKDKKKTR	240
ARKWGER INLAGDVAALNSGLATEAFSAYGNKTDNTREKRTHRRTKRFLSYPRFVEVLVV	
ADNRMVSYHGENLQHYILJIMSIVASIYKDPSIGNLINIVIVNLIVIHNEQDGPSISFNA	360
QITLKNFCQWQHSNSPGGIHHDTAVLL/IRQDICRAHDKCDITLGLAELGITCDPYRSCSIS	
EDSGLSTAFTIAHELGHVFNMPHDDNNKCKEEGVKSPQHVMAPTLNFYINPWMWSKCSRK	480
YITEFLDIGYGECLLNEPESRPYPLPVQLPGILYNVNKQCELIFGPGSQVCPYMMQCRRL	540
WCNNVNGVHKGCRTQHTPWADGTECEPGKHCKYGFCVPKEMDVPVTDGSWGSWSPFGTCS	600
RTCGGGIKTAIRECNRPEPKNGGKYCVGRRMKFKSCNTEPCLKQKRDFRDEQCAHFDGKH	660
FNINGLLPNVRWVPKYSGILMKDRCKLFCRVAGNIAYYQLRDRVIDGIPCGQDINDICVQ	720
GLCRQAGCDHVLNSKARRDKCGVCGGDNSSCKTVAGTFNIVHYGYNTVVRIPAGATNIDV	780
RQHSFSGETDDDNYLALSSSKGEFLLNGNFVVIMAKREIRIGNAVVEYSGSETAVERINS	840
TDRIEQELLLQVLSVGKLYNPDVRYSFNIPIEDKPQQFYWNSHGPWQACSKPCQGERKRK	900
LVCTRESDQLTVSDQRCDRLPQPGHITEPCGTGCDLRWHVASRSECSAQCGLGYRTLDTY	960
CAKYSRLDGKTEKVDDGFCSSHPKPSNREKCSGECNTGGWRYSAWTECSKSCDGGTQRRR	1020
AICVNTRNDVLDDSKCTHQEKVTIQRCSEFPCPQWKSGDWSECLVTCGKGHKHRQVWCQF	1080
GEDRLNDRMCDPETKPTSMQTCQQPECASWQAGPWVQCSVTCGQGYQLRAVKCIIGTYMS	1140
VVDDNDCNAATRPTDTQDCELPSCHPPPAAPETRRSTYSAPRTQWRFGSWIPCSATCGKG	1200
TRMRYVSCRDENGSVADESACATLPRPVAKEECSVTPCGQWKALDWSSCSVTCGQGRATR	1260
QVMCVNYSDHVIDRSECDQDYIPETDQDCSMSPCPQRTPDSGLAQHPFQNEDYRPRSASP	1320
SRTHVLGGNQWRTGPWGACSSTCAGGSQRRVVVCQDENGYTANDCVERIKPDEQRACESG	1380
PCPQWAYGWGECTKLCGGGIRTRLVVCQRSNGERFPDLSCEILDKPPDREQCNTHACPH	1440
DAAWSTGPWSSCSVSCGRGHKQRNVYCMAKDGSHLESDYCKHLAKPHGHRKCRGGRCPKW	1500
KAGAWSQCSVSCGRGVQQRHVGCQIGIHKIARETECNPYTRPESECECQGPRCPLYIWRA	1560
EEWQECTKTCGEGSRYRKVVCVDDNKNEVHGARCDVSKRPVDRESCSLQPCEYVWITGEW	1620
SECSVTCGKGYKQRLVSCSEIYIGKENYEYSYQITINCPGIQPPSVHPCYLRECPVSATW	1680
RVGIWGSCSVSCGVGVMQRSVQCLINEDQPSHLCHIDLKPEERKICRNVYNCELPQNCKE	1740
VKRLKGASEDGEYFLMIRGKLLKIFCAGMHSDHPKEYVTLVHGDSENFSEVYGHRLHNPT	
ECPYNGSRRDDCOCRKDYTAAGFSSFOKIRIDLITSMOI ITTDI OFARTSFCHPVPFATAG	

FIGURE 17 (cc inued)

Pa

DCYSAAKCPQGRFSINLYGTGLSLTESARWISQGNYAVSDIKKSPDGTRVVGKCGGYCGK 1920 CTPSSGTGLEVRVL 1934

10 20 30 40	
tgggggcagcggagggagggtgggaagcaccATGCAGTT 4	10
TGTATCCTGGCCACACTGCTAACGCTCCTGGTGCGGGAC 8	30
CTGGCCGAGATGGGGAGCCCAGACGCCGGGGGGGGGGGG	120
GCAAGGACAGCTGCACCCGAGGCAAGTGAAATTATTAGA 1	160
GACCCIGAGCGAATACGAAATCGIGICICCCATCCGAGIG 2	200
210 220 230 240	•
manda a da a da a da a da a da a da a da	·
AACGCTCTCGGAGAACCCTTTCCCCACGAACGTCCACTTCA 2	240
AAAGAACGCGACGGAGCATTAACTCTGCCACTGACCCCTG 2	280 .
GCCIGCTICGCCICCICTCCICTCCICTACCICCCCC 3	320
CAGGCGCATTACCGCCTCTCTGCCTTCGGCCAGCAGTTTC 3	360
TATTTAATCTCACCGCCAATGCCGGATTTATCGCTCCACT 4	400
410 420 430 440	•
and the land of th	
GITCACIGICACCCTCCTCGGGACGCCCGGGGGAATCAG 4	14 0
ACCAAGITITATICCGAAGAGGAAGCGGAACICAAGCACT 4	480
GITICTACAAAGGCTATGICAATACCAACTCCGAGCACAC	520
GCCGTCATCAGCCTCTGCTCAGGAATGCTGGGCACATTC 5	560
CGGTCTCATGATGGGGGTTATTTTATTGAACCACTACAGT 6	600
610 620 630 640	·
CTATGGATGAACAAGAGAGATGAAGAGGAACAAAACAAA	640
CCACATCATTTATAGGCGCAGCGCCCCCCAGAGAGAGCCCC	680
TCAACAGGAAGCCATGCATGTGACACCTCAGAACACAAAA 7	720
ATAGGCACAGTAAAGACAAGAAGAAAACCAGAGCAAGAAA 7	760
ATGGGGAGAAAGGATTAACCTGGCTGGTGACGTAGCAGCA	800
810 820 830 840	
TTAAACAGCGGCTTAGCAACAGAGGCATTTTCTGCTTATG 8	840
GTAATAAGACQGACAACACAAGAGAAAAGAGGACCCACAG 8	880
AAGGACAAAACGTTTTTTATCCTATCCACGGTTTGTAGAA	920
GICTTGGTGGCAGACAGAATGGTTTCATACCATG	960
GAGAAAACCTTCAACACTATATTTTAACTTTAATGTCAAT 1	1000

FIGURE 17 (col lued)

1010 1020 1030 104	
TGTACCCTCTATCTATAAAGACCCAAGTATTGGAAATTTA	
ATTAATATTGTTATTGTGAACTTAATTGTGATTCATAATG	
AACAGGATGGCCTTCCATATCTTTTAATGCTCAGACAAC	——
ATTAAAAACTTITGCCAGIGGCAGCATTCGAACAGICCA	
GGIGGAATCCATCATGATACTGCTGTTCTCTTAACAAGAC	
1210 1220 1230 124 	
AGGATATCTGCAGAGCTCACGACAAATGTGATACCTTAGG	
CCTGGCTGAACTGGGAACCATTTGTGATCCCTATAGAAGC	
TGITCTATTAGTGAAGATAGTGGATTGAGTACAGCTTTTA	
CGATCGCCCATGAGCTGGCCCATGTGTTTAACATGCCTCA	
TGATGACAACAAATGTAAAGAAGAAGGAGTTAAGAGT	1400
1410 1420 1430 144	10
CCCACCATCHCATCATCATCATCATCATCATCATCATCATCATCATCATC	1440
CCCCAGCATGICATGGCTCCAACACTGAACTTCTACACCA ACCCCTGGATGTGGTCAAAGTGTAGTCGAAAATATATCAC	
TGAGITTTTAGACACIGGITATGCCGAGIGITTGCTTAAC	
GAACCIGAATCCAGACCCIACCCITIGCCIGICCAACIGC	
CAGGCATCCTTTACAACGTGAATAAACAATGTGAATTGAT	
1610 1620 1630 164	
Linder Linder Linder Linder	
TTTTGGACCAGGTTCTCAGGTGTGCCCATATATGATGCAG	1640
TGCAGACGGCTCTGGTGCAATAACGTCAATGGAGTACACA	
AAGGCTGCCGGACTCAGCACACCCTGGGCCGATGGGAC	
GGAGTGCGAGCCTGGAAAGCACTGCAAGTATGGATTTTGT	
GTTCCCAAAGAAATGGATGTCCCCGTGACAGATGGATCCT	1800
1810 1820 1830 184	0
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	
GGGGAAGITGGAGTCCCTTTGGAACCTGCTCCAGAACATG	-
TGGAGGGGCATCAAAACAGCCATTCGAGAGTGCAACAGA CCAGAACCAAAAAATGGTGGAAAATACTGTGTAGGACGTA	
GAATGAAATTTAAGICCTGCAACACGGAGCCATGTCTCAA	
GCAGAAGCGAGACTTCCGAGATGAACAGTGTGCTCACTTT	

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FIGURE 17 (continued)

- 10 commueu)	
,	
2010 2020 2030	2040
GACGGGAAGCATTTTAACATCAACGGTCTGCTTCCC	AATG 2040
TGCGCTGGGICCCTAAATACAGTGGAATTCTGATGA	AGGA 2080
CCGGTGCAAGTTGTTCTGCAGAGTGGCAGGGAACAC	AGCC 2120
TACTATCAGCTTCGAGACAGAGTGATAGATGGAACT	CCIT 2160
GTGGCCAGGACACAAATGATATCTGTGTCCAGGGCC	TITG 2200
2210 2220 2230	2240
<del>malmalmalmalmalmal</del>	
CCGCCAAGCIGGATGCGATCATGTTTTAAACTCAAA	2
CGGAGAGATAAATGCGGGGTTTGTGGTGGCGATAAT	•
CATGCAAAACAGTGGCAGGAACATTTAATACAGTAC	
TGGTTACAATACTGTGGTCCGAATTCCAGCTGGTGC	
AATATTGATGTGCGGCAGCACAGTTTCTCAGGGGAA	ACAG 2400
2410 2420 2430	2440
ACGATGACAACTACTTAGCTTTATCAAGCAGTAAAG	
ATTCTTGCTAAATGGAAACTTTGTTGTCACAATGGC	
ACGGAAATTCCCATTCCGAATCCTGTCGTAGAGTAC	
GGICCGAGACIGCCGIAGAAAGAATTAACTCAACAC	·
CATTGAGCAAGAACTTTTGCTTCAGGTTTTGTCGGT	
2610 2620 2630	2640
AAGITGTACAACCCCGATGTACGCTATTCTTTCAAT	
CAATTGAAGATAAACCTCAGCAGTTTTACTGGAACA	$\cdot$
TGGCCATGCAAGCATGCAGTAAACCCTGCCAAGG CGGAAACGAAAACTTGTTTGCACCAGGGAATCTGAT	
TIACIGITICIGATCAAAGATGCGATCGCTGCCCC	
2810 2820 2830	2840
TGGACACATTACTGAACCCTGTGGTACAGGCTGTGA	
AGGIGGCATGITGCCAGCAGGAGTGAATGTAGTGCC	
GIGGCTTGGGTTACCGCACATTGGACATCTACTGTC	
ATATACCACCTCCATCCCACACTCCACACCTCACACCTTCA	•
GGTTTTTGCAGCAGCCATCCCAAACCAAGCAACCGT	

FIGURE 17 (continued)

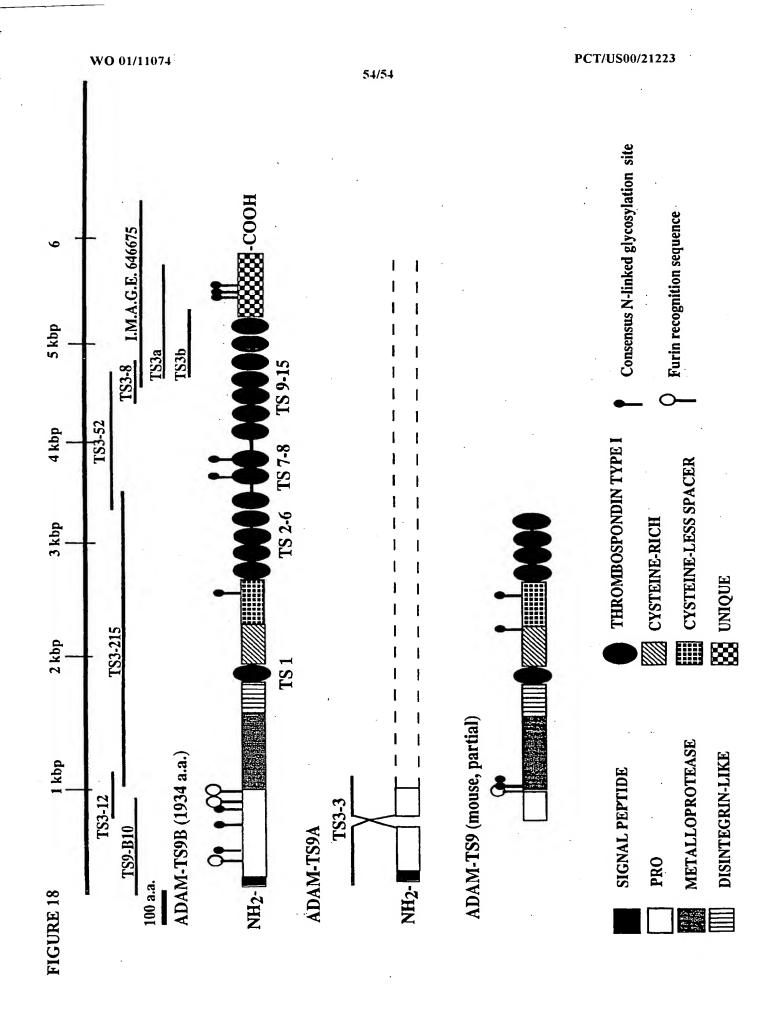
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·	
4010 4020 4030 40	040
CCATGIGCICGGIGGAAACCAGIGGAGAACTGGCCCCTG	G 4040
GGAGCATGTTCCAGTACCTGTGCTGGCGGATCCCAGCGG	C 4080
GIGITGITGIATGICAGGATGAAAATGGATACACCGCAA	A 4120
CGACTGTGTGGAGAGAATAAAACCTGATGAGCAAAGAGC	C 4160
TGTGAATCCGGCCCTTGTCCTCAGTGGGCTTATGGCAAC	T 4200
4210 4220 4230 42	240
<del>matrial matrial and a second control and a second </del>	<u></u>
GGGGGGGGCACTAAGCTGTGTGGTGGAGGCATAAGAA	C 4240
AAGACTOGTOGTCTGTCAGCGGTCCAACGGTGAACGGTT	T 4280
CCAGATTTGAGCTGTGAAATTCTTGATAAACCTCCCGAT	C 4320
GIGACCAGIGIAACACACATCCITGICCACACGACCCIG	C 4360
ATGGAGTACTGGCCCTTGGAGCTCGTGTTCTGTCTCTTG	T 4400
1120 1120 1	440
	•
GGTCGAGGCATAAACAACGAAATGTTTACTGCATGGCA	·
AAGATGGAAGCCATTTAGAAAGTGATTACTGTAAGCACC	
GCTAACCCACATGGCCACAGAAGTGCCGAGGAGGAAG	:
TGCCCCAAATGGAAAGCTGGCGCTTGGAGTCAGTGCTCT	
TGTCCTGTGGCCGAGGCGTACAGCAGAGGCATGTGGGCT	rg 4600
1010	640
	Ц
TCAGATCGGAACACACAAAATAGCCAGAGAGACCGAGTG	
AACCCATACACCAGACCGGAGTCGGAATGCCAA	•
GCCCACGGTGTCCCCTTTACACTTGGAGGGCAGAGGAAT	•
GCAAGAATGCACCAAGACCTGCGGCGAAGGCTCCAGGTA	
CGCAAGGTGGTGTGTGGATGACAACAAAACGAGGTG	C 4800
4810 4820 4830 4	840
	<u> </u>
ATGGGGCACGCTGTGACGTGAGCAAGCGGCCGGTGGACC	OG 4840
TGAAACCTGTAGTTTCCAACCCTCCGAGTATGTCTGGAT	
ACAGGAGAATGGTCAGAGTGCTCAGTGACCTGTGGAAA	
GCTACAAACAAAGGCTTGTCTCGTGCAGCGAGATTTACA	
CGGGAAAGAGAATTATGAATACAGCTACCAAACCACCAI	IC 5000

FIGURE 17 (cc nued)

5010 5020 5030 5040
<u> </u>
AACTGCCCAGGCAGCCCCCCAGTGTTCACCCCTGTT 5040
ACCIGAGGGAGIGCCCIGICICGGCCACCIGGAGAGIIGG 5080
CAACIGGGGAGCIGCICAGIGICITGIGGIGITGGAGIG 5120
ATGCAGAGATCTGTGCAATGTTTAACCAATGAGGACCAAC 5160
CCAGCCACTTATGCCACACTGATCTGAAGCCAGAAGAACG 5200
5210 5220 5230 5240
<u> </u>
AAAAACCTGCCGTAATGTCTATAACTGTGAGTTACCCCAG 5240
AATTGCAAGGAGTAAAAAGACTTAAAGGTGCCAGTGAAG 5280
ATGGTGAATATITCCTGATGATTAGAGGAAAGCTTCTGAA 5320
GATATTCTGTGCGGGGATGCACTCTGACCACCCCAAAGAG 5360
TACGIGACACIGGIGCATGGAGACICIGAGAATTICICCG 5400
5410 5420 5430 5440
<u> </u>
AGGITTATGGCCACAGGITACACAACCCAACAGAATGICC 5440
CTATAACGGGAGCCGCGATGACTGCCAATGTCGGAAG 5480
GATTACACGCCCCCCGGTTTTCCAGTTTTCAGAAAATCA 5520
GAATAGACCTGACCAGCATGCAGATAATCACCACTGACTT 5560
ACAGTTTGCAAGGACAAGGACATCCCGTCCCTTTT 5600
5610 5620 5630 5640
<u> </u>
GCCACAGCCGGGGATTGCTACAGCGCTGCCAAGTGCCCAC 5640
AGGGTCGTTTTAGCATCAACCTTTATGGAACCGCCTTGTC 5680
TTTAACTGAATCTGCCAGATGGATATCACAAGGGAATTAT 5720
GCTGTCTCTGACATCAAGAAGTCGCCGGATGGTACCCGAG 5760
TCGTAGGGAAATGCGGTGGTTACTGTGGAAAATGCACTCC 5800
5810 5820 5830 5840
<u> </u>
ATCCTCTGGTACTGGCCTGGAGGTGCGAGTTTTAtagcta 5840
aggtgctttgaagaggaagccattatggatggatgaagga 5880
tagtaatgcaatacctccaccttaatttgggtgcatgtgt 5920
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   <211> 3002
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   <213> mus musculus ADAMTS-5
   <220>
   <221> CDS
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                   Met Arg Leu Glu Trp Ala Ser Leu Leu Leu
30
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   Leu Leu Leu Ser Ala Ser Cys Leu Ser Leu Ala Ala Asp Ser Pro
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	Leu I 130				135					.140					
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			Leu	980	_		-	-	985				-	990		
25			Сув 995				1	1000			_	_ 1	.005	-	•	•
	3	1010	Cys			1	1015	-	_	_	1	1020				
	1025	5 .	Gln		_ 1	1030	_	_		. 1	1035	_		-		040
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1560

Ser Glu Cys Ser Val Thr Cys Gly Lys Gly Tyr Lys Gln Arg Leu Val

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the way

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				500				-	505					510		Trp
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14 SALESTAN

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	Arg Pro His Cys Leu Tyr Ala Gly His Leu Gln Gly Gln Ala Ser Ser	
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	Arg I	Leú	His 35	Pro	Arg	Gln	'Val	Lys 40	Leu	Leu	Glu	Thr	Leu 45	Ser	Glu	Tyr	
65	Glu :	Ile	Val	Ser	Pro	Ile	Arg	Val	Asn	Ala	Leu	Gly	Glu	Pro	Phe	Pro	•

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5	Thr 65	Asn	Val	His	Phe	Lys 70	Arg	Thr	Arg	Arg	Ser 75	Ile	Asn	Ser	Ala	Th:
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•	Glu	His	Thr	Ala	Val 165	Ile	Ser	Leu	Cys	Ser 170	Gly	Met ,	Leu	Gly	Thr 175	Phe
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55	Ile	Asn	Ile	Val 340	Ile	Val	Asn	Leu	Ile 345	Val	Ile	His	Asn	Glu 350	Gln	Asp
	Gly	Pro	Ser 355	Ile	Ser	Phe	Asn	Ala 360	Gln	Thr	Thr	Leu	Lys 365	Asn	Phe	Cys
60	Gln	Trp 370	Gln	His	Ser	Asn	Ser 375	Pro	Gly	Gly	Ile	His 380	His	Asp	Thr	Ala
65	Val 385	Leu	Leu	Thr	Arg	Gln 390	Asp	Ile	Cys	Arg	Ala 395	His	Asp	Lys	Cys	As ₁
	Thr	Len	Gly	T.O.	λla	G111	T.Ou	Glv	Th~	Tla	Cyc	Acn	Dro	T's	7	C

					405					410					415	
-	Cys	Ser	Ile	Ser 420	Glu	Asp	Ser	Gly	Leu 425	Ser	Thr	Ala	Phe	Thr 430	Ile	Ala
5	His	Glu	Leu 435	Gly	His	Val	Phe	Asn 440	Met	Pro	His	Asp	Asp 445	Asn	Asn	Lys
10	Cys	Lys 450	Glu	Glu	Gly	Val	Lys 455	Ser	Pro	Gln		Val 460	Met	Ala	Pro	Thr
	Leu 465	Asn	Phe	Tyr	Thr	Asn 470	Pro	Trp	Met	Trp	Ser 475	Lys	Cys	Ser	Arg	Lys 480
15	Tyr	Ile	Thr	Glu	Phe 485	Leu	Asp	Thr	Gly	Tyr 490	Gly	Glu	Сув	Leu	Leu 495	Asn
20	Glu	Pro	Glu	Ser 500	Arg	Pro	Tyr	Pro	Leu 505	Pro	Val	Gln	Leu	Pro 510	Gly	Ile
20	Leu	Tyr	Asn 515	Val	Asn	Lys	Gln	Сув 520	Glu	Leu	Ile	Phe	Gly 525	Pro	Gly	Ser
25	Gln	Val 530	Cys	Pro	Tyr	Met	Met 535	Gln	Cya	Arg	Arg	Leu 540	Trp	Ser	Asn	Asn
	Val 545	Asn	Gly	Val	His	Lys 550	Gly	Cys	Arg	Thr	Gln 555	His	Thr	Pro	Trp	Ala 560
30	Asp	Gly	Thr	Glu	Сув 565	Glu	Pro	Gly	Lys	His 570	Сув	Lys	Tyr	Gly	Phe 575	Cys
35	Val	Pro	Lys	Glu 580	Met	Asp	Val	Pro	Val 585	Thr	Asp	Gly	Ser	Trp 590	Gly	Ser
33	Trp	Ser	Pro 595	Phe	Gly	Thr	Cys	Ser 600	Arg	Thr	Сув	Gly	Gly 605	Gly	Ile	Lys
40	Thr	Ala 610	Ile	Arg	Glu	Cys	Asn 615	Arg	Pro	Glu	Pro	Lys 620	Asn	Gly	Gly	Lys
	Tyr 625	Сув	Val	Gly	Arg	Arg 630	Met	Ìуs	Phe	Lys	Ser 635	Cys	Asn	Thr	Glu	Pro 640
45	Cys	Leu	Lys	Gln	Lys 645	Arg	Asp	Phe	Arg	Asp 650	Glu	Gln	Cys	Ala	His 655	Phe
50	Asp	Gly	Lys	His 660	Phe	Asn	Ile	Asn	Gly 665	Leu	Leu	Pro	Asn	Val 670	Arg	Trp
	Val	Pro	Lys 675	Tyr	Ser	Gly	Ile	Leu 680	Met	Lys	Asp	Arg	Cys 685	Lys	Leu	Phe
55	Cys	Arg 690		Ala	Gly	Asn	Thr 695	Ala	Tyr	Tyr	Gln	Leu 700	Arg	Asp	Arg	Val
	Ile 705	Asp	Gly	Thr	Pro	Cys 710	Gly	Gln	Asp	Thr	Asn 715	Asp	Ile	Cys	Val	Gln 720
60	Gly	Leu	ÇVa	Arg	Gln 725	Ala	Gly	Cys	Asp	His 730	Val	Leu	Asn	Ser	Lys 735	Ala
65		Arg	Asp	Lys 740		Gly	Val	Cys	Gly 745		Asp	Asn	Ser	Ser 750	Суѕ	Lys
		Val	Ala	Gly	Thr	Phe	Asn	Thr	'Val	His	Tyr	Glý	Tyr	Asn	Thr	Val

			755					760					765			
5	Val	Arg 770	Ile	Pro	Ala	Gly	Ala 775	Thr	Asn	Ile	Aap	Val 780	Arg	Gln	His	Ser
	Phe 785	Ser	Gly	Glu	Thr	Asp 790	Asp	Asp	Asn	Tyr	Leu 795	Ala	Leu	Ser	Ser	Ser 800
10	Lys	Gly	Glu	Phe	Leu 805	Leu	Asn	Gly	Asn	Phe 810	Val	Val	Thr	Met	Ala 815	Lys
÷	Arg	Glu	Ile	Arg 820	Ile	Gly	Asn	Ala	Val 825	Val	Glu	Tyr	Ser	Gly 830	Ser	Glu
15	Thr	Ala	Val 835	Glu	Arg	Ile	Asn	Ser 840	Thr	Asp	Arg	Ile	Glu 845	Gln	Glu	Leu
20	Leu	Leu 850	Gln	Val	Leu	Ser	Val 855	Gly	Lys	Leu	Tyr	Asn 860	Pro	Asp	Val	Arg
20	Tyr 865	ser	Phe	Asn	Ile	Pro 870	Ile	Glu	Asp	Lys	Pro 875	Gln	Gln	Phe	Tyr	Trp 880
25	Asn	Ser	His	Gly	Pro 885	Trp	Gln	Ala	Cys	Ser 890	Lys	Pro	Cys	Gln	Gly 895	Glu
	Arg	Lys	Arg	Lys 900	Leu	Val	Cys	Thr	Arg 905	Glu	Ser	Asp	Gln	Leu 910	Thr	Val
30	Ser	Asp	Gln 915	Arg	Cys	Asp	Arg	Leu 920	Pro	Gln	Pro	Gly	His 925	Ile	Thr	Glu
35	Pro	Cys 930	Gly	Thr	Gly	Cys	Asp 935	Leu	Arg	Trp	His	Val 940	Ala	Ser	Arg	Ser
,,,	Glu 945	Cys	Ser	Ala	Gln	Cys 950	Gly	Leu	Gly	Tyr	Arg 955	Thr	Leu	Asp	Ile	Tyr 960
40	Сув	Ala	Lys	Tyr	Ser 965	Arg	Leu	Asp	Gly	Lys 970	Thr	Glu	Lys	Val	Asp 975	Asp
	Gly	Phe	Cys	Ser 980	Ser	His	Pro	Lys	Pro 985	Ser	Asn	Arg	Glu	Lys 990	Cys	Ser
45	Gly	Glu	Cys 995	Asn	Thr	Gly		Trp 1000	Arg	Tyr	Ser		Trp 1005	Thr	Glu	Cys
50		Lys 1010	Ser	Cys	Asp		Gly 1015	Thr	Gln	Arg		Arg L020	Ala	Ile	Cys	Val
	Asn 1029		Arg	Asn		Val 1030	Leu	Asp	Asp		Lys 1035	Сув	Thr	His		Glu L040
55	Lys	Val	Thr		Gln L045	Arg	Cys	Ser		Phe L050	Pro	Cys	Pro	Gln	Trp 1055	Lys
	Ser	Gly		Trp 1060	Ser	Glu	Cys		Val 1065	Thr	Cys	Gly	_	Gly 1070	His	Lys
60	His		Gln 1075	Val	Trp	Cys		Phe 080	Gly	Glu	Asp		Leu 1085	Asn	Asp	Arg
65		Cys 1090	Asp	Pro	Glu		Lys 1095	Pro	Thr	Ser		Gln L100	Thr	Cys	Gln	Gln
-	Pro	Glu	Met	Ala	Ser	Trp	Gln	Ala	Gly	Pro	Trp	Val	Gln	Cys	Ser	Val

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5	Thr	Cys	Gly		Gly 125	Tyr	Gln	Leu		Ala 130	Val	Lys	Суз		Ile 135	Gly
3	Thr	Tyr		Ser 140	Val	Val	Asp		Asn 145	Asp	Cys	Asn		Ala 150	Thr	Arg
10	Pro		Asp .155	Thr	Gln	Asp		Glu 160	Leu	Pro	Ser		His .165	Pro	Pro	Pro
		Ala 170	Pro	Glu	Thr		Arg	Ser	Thr	Tyr		Ala 180	Pro	Arg	Thr	Gln
15	Trp 1185	_	Phe	Gly		Trp 190	Thr	Pro	Cys		Ala 195	Thr	Cys	Gly	Lys 1	Gly 200
20				_1	1205				ָב	1210				1	Val 1215	
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25		1	.235				1	1240				1	.245		Ser	
	1	250			-	_ 1	1255				1	260			Met	
30	1265	5	-		1	1270				1	1275					280
3 5	_			1	1285				1	1290				1	Pro 1295	
			1	1300				1	1305				1	.310	Glu	
40		1	315				1	1320				1	1325		Gly	
4 -	3	1330	•	_		- 1	1335	•	_		_ 1	1340			Cys	
* >	1349	5			- 3	1350				1	1355					360
50				:	1365				1	L370				1	Arg 1375 Gly	
	-		1	1380		•		3	1385		-	-	1	1390	Val	
55		1	1395		-	_	•	1400		_		_ 1	1405		Ile	•
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_	Ser	His 1	Leu 475	Glu	Ser	Asp		Cys 480	Lys	His	Leu		Lys 1485	Pro	His	Gly
5		Arg	Lys	Сув	Arg		Gly 495	Arg	Cys	Pro		Trp L500	Lys	Ala	Gly	Ala
10	Trp 1509	Ser	Gln	Cys		Val 510	Ser	Cys	Gly		Gly 1515	Val	Gln	Gln		His 520
	Val	Gly	Cys		Ile 1525	Gly	Thr	His		11e .530	Ala	Arg	Asp		Glu 1535	Cys
15	Asn	Pro		Thr 1540	Arg	Pro	Glu		Glu .545	Cys	Glu	Cys		Gly 1550	Pro	Arg
20	Cys	Pro 1	Leu .555	Tyr	Thr	Trp		Ala L560	Glu	Glu	Ser		Glu 1565	Cys	Thr	Lys
		Cys 1570	Gly	Glu	Gly		Arg 575	Tyr	Arg	Lys		Val 1580	Cys	Val	Asp	Asp
25	Asn 1589	Lys 5	Asn	Glu		His 590	Gly	Ala	Arg		Asp L595	Val	Ser	Lys		Pro L600
	Val	Asp	Arg		Ser 1605	Cys	Ser	Leu		Pro 1610	Сув	Glu	Tyr		Trp 1615	Ile
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33		Tyr 1650	Ser	Tyr	Gln		Thr 1655	Ile	Asn	Суѕ		Gly 1660	Thr	Gln	Pro	Pro
40	Ser 166	Val 5	His	Pro		Tyr 1670	Leu	Arg	Glu		Pro 1675	Val	Ser	Ala		Trp 1680
	Arg	Val	Gly		Trp 1685	Gly	Ser	Cys		Val 1690	Ser	Cys	Gly		Gly 1695	Val
45	Met	Gln		Ser 1700	Val	Gln	Сув		Thr 1705	Asn	Glu	Asp		Pro 1710	Ser	His
50	Leu	Суѕ	His 1715	Thr	Asp	Leu		Pro 1720	Glu	Glu	Arg		Thr 1725	Cys	Arg	Asn
		Tyr 1730	Asn	Сув	Glu		Pro 1735	Gln	Asn	Сув		Glu 1740	Val	Lys	Arg	Leu
55	Lys 174	Gly 5	Ala	Ser		Авр 1750	Gly	Glu	Tyr		Leu 1755		Ile	Arg		Lys 1760
	Leu	Leu	Lys		Phe 1765	Cys	Ala	Gly		His 1770		Asp	His		Lys 1775	Glu
60	Tyr	Val		Leu 1780		His	Gly		Ser 1785	Glu	Asn	Phe	Ser	Glu 1790		Туг
65	_	His	Arg 1795		His	Asn		Thr 1800	Glu	Cys	Pro	Tyr	Asn 1805		Ser	Arg
55		Asp	Asp	Cys	Gln	Cys	Arg	Lys	Asp	Tyr	Thr	Ala	Ala	Gly	Phe	Sei

1810 1815 1820

Ser Phe Gln Lys Ile Arg Ile Asp Leu Thr Ser Met Gln Ile Ile Thr 1825 1830 1835 1840

Thr Asp Leu Gln Phe Ala Arg Thr Ser Glu Gly His Pro Val Pro Phe 1845 1850 1855

Ala Thr Ala Gly Asp Cys Tyr Ser Ala Ala Lys Cys Pro Gln Gly Arg 10 1860 1865 1870

Phe Ser Ile Asn Leu Tyr Gly Thr Gly Leu Ser Leu Thr Glu Ser Ala 1875 1880 1885

15 Arg Trp Ile Ser Gln Gly Asn Tyr Ala Val Ser Asp Ile Lys Lys Ser 1890 1895 1900

Pro Asp Gly Thr Arg Val Val Gly Lys Cys Gly Gly Tyr Cys Gly Lys 1905 1910 1915 1920

Cys Thr Pro Ser Ser Gly Thr Gly Leu Glu Val Arg Val Leu 1925 1930

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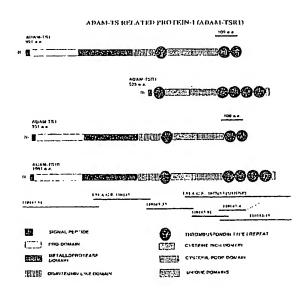
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(54) Title: NUCLEIC ACIDS ENCODING ZINC METALLOPROTEASES



(57) Abstract: Isolated mammalian proteins having disintegrin-like and metalloprotease domains with thrombospondin type I motifs, i.e., ADAMTS proteins, are provided. The proteins are ADAMTS-5, ADAMTS-6, ADAMTS-7, ADAMTS-8, ADAMTS-9 and ADAMTS-10, collectively referred to as "ADAMTS-N". The present invention also provides isolated polynucleotides which encode an ADAMTS-N protein or a variant thereof, polynucleotide sequences complementary to such polynucleotides, vectors containing such polynucleotides, and host cells transformed or transfected with such vectors. The present invention also relates to antibodies which are immunospecific for one or more of the ADAMTS-N proteins. The present invention also relates to a protein referred to hereinafter as ADAMTS-R1 (ADAM-TS Related protein-1) and the polynucleotides which encode such protein.



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#### NUCLEIC ACIDS ENCODING ZINC METALLOPROTEASES

#### Background of the Invention

This invention relates to isolated nucleic acid -molecules

which encode proteins belonging to a zinc metalloprotease family.

The zinc metalloproteases have been implicated in a variety of diseases and development disorders that involve* enhanced or depressed proteolysis of components of the extracellular matrix, receptors, or other extracellular molecules.

More particularly, the invention relates to isolated nucleic acid molecules encoding proteins belonging to a subfamily of zinc metalloproteases referred to as "ADAMTS", an abbreviation for A Disintegrin-like And Metalloprotease domain with ThromboSpondin type I motifs. Proteins in the ADAMTS subfamily all possess a Zn protease catalytic site consensus sequence (HEXXH+H), which suggests an intact catalytic activity for each of these proteins. The ADAMTS proteins also have putative N-terminal signal peptides and lack transmembrane domains, which suggests that the proteins in this subfamily are secreted. The proteins in the ADAMTS subfamily also possess at least one thrombospondin type (TSP1) motif, which suggests a binding of these proteins to components of the extracellular matrix (ECM) or to cell surface components.

Members of the ADAMTS subfamily of proteins are ADAMTS-1,

ADAMTS-2, ADAMTS-3, and ADAMTS-4. ADAMTS-1 protein is selectively

25 expressed in colon 26 adenocarcinoma cachexigenic sublines. ADAMTS-1

mRNA is induced by the inflammatory cytokine interleukin-1 in vitro

and by intravenous administration of lipopolysaccharide in vivo.

Thus, the ADAMTS-1 protein is believed to play a role in tumor

cachexia and inflammation.

The ADAMTS-2 protein is also known as procollagen I/H aminopropetide processing enzyme or PCINP. The ADAMTS-2 protein catalyzes cleavage of native triple-helical procollagen I and procollagen II.

The ADAMTS-2 protein also has an affinity for collagen XIV. Lack of the ADAMTS-2 protein is known to cause dermatosparaxis in cattle, or Ehlers-Danlos syndrome type VIIC (EDS-VIIC) in humans. EDS-VIIC is 5 characterized clinically by severe skin fragility, and biochemically by the presence in skin of procollagen which is incompletely processed at the amino terminus. Thus, it is believed that the ADAMTS-2 protein plays a role in processing of procollagen to mature collagen, an essential step for correct assembly of collagen into 
10 collagen fibrils. The ADAMTS-3 protein is similar in sequence to ADAMTS-2 and may have similar function.

The ADAMTS-4 protein catalyzes cleavage of the core protein of the extracellular matrix proteoglycan, aggrecan. Aggrecan degradation is an important factor in the erosion of articular cartilage in arthritic disease. Aggrecan fragments have been identified in cultures undergoing cartilage matrix degradation and in arthritic synovial fluids. Therefore, overexpression or activation 10 of ADAMTS-4 protein may be related to both inflammatory and non-inflammatory arthritis.

- On the basis of the structure, location, and the demonstrated proteolytic activity of ADAMTS proteins 1-4, it is expected that other members of the ADAMTS subfamily play a role in the cleavage of proteoglycan core proteins that are found in the extracellular matrix, such as, for example, versican, brevican, neuracan, NG-2,
- 25 aggrecan, as well as molecules such as collagen. It is also expected that other members of the ADAMTS subfamily play a role in embryogenesis, implantation of a fertilized egg, angiogenesis, arthritic degradation of cartilage, inflammation, nerve regeneration, tumor growth, and metastases.
- 30 Thus, it is desirable to have other members of the ADAMTS

subfamily of proteins, the nucleic acids that encode such proteins, and antibodies that are specific for such proteins. Such molecules are useful research tools for studying development of the extracellular matrix during embryogenesis and fetal development, and for studying disorders or diseases that are characterized by improper development of the extracellular matrix or enhanced or reduced destruction of the extracellular matrix. Such molecules, particularly the nucleic acids and the antibodies, are also useful tools for diagnosing such diseases or for monitoring the efficacy of therapeutic agents that have been developed to treat such diseases.

#### Summary of the Invention

The present invention provides novel, isolated, and substantially purified proteins having the characteristics of an 15 ADAMTS protein. The novel proteins are referred to hereinafter individually as "ADAMTS-5", "ADAMTS-6", "ADAMTS-7", "ADAMTS-8", "ADAMTS-9" and "ADAMTS-10", and collectively as "ADAMTS-N". In one embodiment, the ADAMTS-5 protein is a mature mouse protein which comprises amino acid 231 through amino acid 930 of the sequence set 20 forth set forth in SEQ ID NO: 2. In another embodiment, ADAMTS-5 is a human ADAMTS-5 protein which comprises amino acid 1 through amino acid 518 of the sequence set forth in SEQ ID NO: 4. In one embodiment, mature human ADAMTS-6 protein comprises amino acid 245 through amino acid 860 of SEQ ID NO: 6. In one embodiment, mature 25 human ADAMTS-7 protein comprises amino acid 233 through amino acid 997 of the sequence set forth in SEQ ID NO: 8. In one embodiment, mature ADAMTS-8 protein is a mouse protein which comprises amino acid 229 through amino acid 905 of the sequence set forth in SEQ ID NO: 10. In another embodiment, ADAMTS-8 protein is a human protein which 30 comprises amino acid 1 through amino acid 245 of the sequence set forth in SEQ ID NO: 12. In one embodiment, mature ADAMTS-9 protein

is a human protein which comprises amino acid 236 through amino acid 1882 of the sequence set forth in SEQ ID NO: 14. In another embodiment, ADAMTS-9 protein is a mouse protein which comprises amino acid 1 through amino acid 974 of the sequence set forth in SEQ ID NO:

- 5 16. In one embodiment, mature ADAMTS 10 protein is a human protein which comprises amino acid 212 through amino acid 1081 of the sequence set forth in SEQ ID NO: 18. In another embodiment, ADAMTS-10 protein is a mouse protein which comprises amino acid 1 through amino acid 547 of the sequence set forth in SEQ ID NO: 20.
- The present invention also provides isolated polynucleotides which encode an ADAMTS-N protein or a variant thereof, polynucleotide sequences complementary to such polynucleotides, vectors containing such polynucleotides, and host cells transformed or transfected with such vectors. The present invention also relates to antibodies which are immunospecific for one or more of the ADAMTS-N proteins. The
  - present invention also relates to a protein referred to hereinafter as ADAMTS-R1 (ADAM-T-S Related protein-1) and the polynucleotides which encode such protein. In one embodiment, the ADAMTS-R1 protein comprises amino acid 1 through amino acid 525 of the sequence set
- Brief Description of the Drawings
  Figure 1 shows an amino acid sequence (SEQ ID NO:2) of a full-length
  mouse ADAMTS-5 protein and a nucleic acid sequence (SEQ ID NO: 1)

which encodes such protein.

20 forth in SEQ. ID NO: 22.

- 25 Figure 2 shows an amino acid sequence (SEQ ID NO:4) of a partial human ADAMTS-5 protein and a nucleic acid sequence (SEQ ID NO: 3) which encodes such protein.
- Figure 3 shows an amino acid sequence (SEQ ID NO:6) of a full-length human ADAMTS-6 protein and a nucleic acid sequence (SEQ ID NO:5)

  30 which encodes such protein.

Figure 4 shows an amino acid sequence (SEQ ID NO:8) of a full-length human ADAMTS-7 protein and a nucleic acid sequence (SEQ ID NO:7) which encodes such protein.

Figure 5 shows an amino acid sequence (SEQ ID NO: 10) of a full-

5 length mouse ADAMTS-8 protein and a nucleic acid sequence (SEQ ID NO:9) which encodes such protein.

Figure 6 shows an amino acid sequence (SEQ ID NO: 12) of a partial human ADAMTS-8 protein and a nucleic acid sequence (SEQ ID NO: 11) which encodes such amino acid sequence.

10 Figure 7 shows an amino acid sequence (SEQ ID NO: 14), of a full-length human ADAMTS-9 protein and a nucleic acid sequence (SEQ ID NO: 13) Which encodes such protein.

Figure 8 shows an amino acid sequence (SEQ ID NO: 16) of a partial mouse ADAMTS-9 protein and a nucleic acid sequence (SEQ ID NO: 15)

15 which encodes such amino acid sequence.

Figure 9 shows an amino acid sequence (SEQ ID NO:18) of a full-length human ADAMTS-10 protein and a nucleic acid sequence (SEQ ID NO: 17) which encodes such protein.

Figure 10 show's an amino acid sequence (SEQ ID NO:20) of a partial 20 mouse ADAMTS-10 protein and a nucleic acid sequence (SEQ ID NO: 19) which encodes such amino acid sequence.

Figure 11 shows an amino acid sequence (SEQ ID NO:22) of a full length ADAMTS-R1 protein and a nucleic acid sequence (SEQ ID NO: 21) which encodes such protein.

25 Figure 12 depicts the cloning strategy used for isolation of a. mouse and human ADAMTS-5 cDNAs b. human ADAMTS-6 cDNA and c. human ADAMTS-7 cDNA. The domain organization of each protein relative to the cDNA clones (thin line) is shown as is the extent of overlap between clones. The original I.M.A.G.E. clones are underlined. Intronic 30 regions of incompletely spliced transcripts are shown by the angled

- Ass. Strainer

dotted lines. DNA scale marker (in bp) and amino acid scale marker are at upper right. Location of the probe used for in situ hybridization (ISH) is shown in a.

Figure 13 shows the predicted amino acid sequences of a. the mouse 5 and human ADAMTS-5 proteins (alignment shows mouse sequence above, partial human sequence below) b. ADAMTS-6, and c. ADAMTS-7. The active-site sequences and proposed Met-turn are enclosed in boxes.

· Potential furin cleavage site(s) are indicated by arrows.

Thrombospondin type-1 modules are underlined. Potential sites for N-

- 10 inked glycosylation are overlined. Cysteine residues within the context of an MMP-like "cysteine switch" are indicated by the solid circles. Other cysteine residues are indicated by asterisks. The prodomain extends until the furin cleavage site, and the catalytic domain extends from the furin cleavage site to the approximate start
- 15 of the disintegrin-like sequence (Dis). The start of the spacer domain is indicated; the region between the N-terminal TS domain and the spacer domain is the cysteine-rich domain. The single letter amino acid code is used.

Figure 14 shows Northern analysis of expression of ADAMTS-5, 6 and 7.

- 20 RNA kilobase markers are shown at left of each autoradiogram, and tissue origin is indicated above each lane. a. Mouse embryo northern blots. b. Human multiple adult tissue northern blots.
  - Figure 15 is a schematic representation of the domain structure of ADAMTS-R1 protein as compared to ADAMTS-1 protein.
- 25 Figure 16 shows an amino acid sequence (SEQ ID NO: 24) of an alternative embodiment of a full-length human ADAMTS-10 protein and a nucleic acid sequence (SEQ ID NO: 23) which encodes such protein.

  Figure 17 shows an amino acid sequence (SEQ ID NO: 26) of an alternative embodiment of human ADAMTS-9, which is a full-length

  30 protein designated as human ADAMTS-9b and a nucleic acid sequence

(SEQ ID NO: 25) which encodes such protein.

Figure 18 is a schematic representation of the domain structure of human ADAMTS-9b protein as compared to human and mouse ADAMTS-9 protein.

## Detailed Description of the Invention

The present invention relates to novel, isolated, substantially purified, mammalian proteins belonging to the ADAMTS subfamily of metalloproteases. As used herein, the term "substantially purified" 10 refers to a protein that is removed from its natural environment, isolated or separated, and at least 60% free, preferably 75% free, and most preferably 90% free from other components with which it is naturally associated.

The novel mammalian proteins are ADAMTS-5, ADAMTS-6, ADAMTS-7, 15 ADAMTS-8, ADAMTS-9 and ADAMTS-10, collectively ADAMTS-N. In one embodiment, the ADAMTS-5 protein is a mature mouse protein which comprises amino acid 231 through amino acid 930 of the sequence set forth in SEQ ID NO: 2. In another embodiment, the ADAMTS-5 protein is a human protein which comprises amino acid 1 through amino acid 20 518 of the sequence set forth in SEQ ID NO: 4. In one embodiment, ADAMTS-6 protein is a mat-Lire human protein which comprises amino acid 245 through amino acid 860 of SEQ ID NO:6. In one embodiment, the ADAMTS-7 protein is a mature human protein which comprises amino acid 233 through amino acid 997 of the sequence set forth in SEQ ID 25 NO: 8. In one embodiment, the ADAMTS-8 protein is a mature mouse protein which comprises amino acid 229 through amino acid 905 of the sequence set forth in SEQ ID NO: 10. In another embodiment, the ADAMTS-8 protein is a human protein which comprises amino acid 1 through amino acid 245 of the sequence set forth in SEQ ID NO: 12. 30 In one embodiment, the ADAMTS-9 is a mature human protein which comprises amino acid 236 through amino acid 1882 of the sequence set

forth in SEQ ID NO: 14. In another embodiment, the ADAMTS-9 protein is a mouse protein which comprises amino acid 1 through amino acid 874 of the sequence set forth in SEQ ID NO: 16. In another embodiment, the ADAMTS-9 designated ADAMTS-9b is a human protein 5 which is comprised of 1934 amino acids as set forth in SEQ ID NO 26. In one embodiment, the ADAMTS-10 protein is a mature human protein which comprises amino acid 212 through amino acid 1081 of the sequence set forth in SEQ ID NO: 18. In another embodiment the ADAMTS- 10 protein is a mouse protein which comprises amino acid 1... 10 through amino acid 525 of the sequence set forth in SEQ ID NO:20. In another embodiment, the ADAMTS-10 protein is a human protein which is comprised of 1072 amino acids as set forth in SEQ ID NO 24.

All of the novel ADAMTS-N proteins starting at the amino terminus comprise a signal sequence followed by a putative pro region 15 which contains a consensus sequence for furin cleavage (except for ADAMTS-10), a catalytic domain, a domain of 60-90 residues with 35 to 45% similarity to snake venom disintegrins, a TS module, a cysteine rich domain containing multiple conserved cysteine residues, a spacer domain, and one or multiple C terminal TS modules. (See Figure 12.)

20 As determined using the BLAST software from the National Center for Biotechnology Information, the predicted mature forms of the ADAMTS-N proteins show an overall 20-30% similarity to each other and to ADAMTS-1-4, although this may be considerably higher or lower for individual domains as described below.

25 The ADAMTS-N proteins also encompass variants of the ADAMTS-N proteins shown in Figs. 1-10. A "variant" as used herein, refers to a protein whose amino acid sequ nce is similar to one of the amino acid sequences shown in Figs. 1-10, hereinafter referred to as the reference amino acid sequence, but does not have 100% identity with 30 the reference sequence. The variant protein has an altered sequence

in which one or more of the amino acids in the reference sequence is deleted or substituted, or one or more amino acids are inserted into the sequence of the reference amino acid sequence. As a result of the alterations, the variant protein has an amino acid sequence which 5 is at least 95% identical to the reference sequence, preferably, at least 97% identical, more preferably at least 98% identical, most preferably at least 99% identical to the reference sequence. Variant sequences which are at least 95% identical have no more than 5 alterations, i.e. any combination of deletions, insertions or 10 substitutions, per 100 amino acids of the reference sequence. Percent identity is determined by comparing the amino acid sequence of the variant with the reference sequence using MEGALIGN project in the DNA STAR program. Sequences are aligned for identity calculations using the method of the software basic local alignment 15 search tool in the BLAST network service (the National Center for Biotechnology Information, Bethesda, MD) which employs the method of Altschul, S. F., Gish, W., Miller, W., Myers, E. W. & Lipman, D. J. (1990) J. Mol. Biol. 215, 403-410. Identities are calculated by the Align program (DNAstar, Inc.) In all cases, internal gaps and amino 20 acid insertions in the candidate sequence as aligned are not ignored when making the identity calculation.

while it is possible to have nonconservative amino acid substitutions, it is preferred that the substitutions be conservative amino acid substitutions, in which the substituted amino acid has similar structural or chemical properties with the corresponding amino acid in the reference sequence. By way of example, conservative amino acid substitutions involve substitution of one aliphatic or hydrophobic amino acids, e.g. alanine, valine, leucine and isoleucine, with another; substitution of one hydroxyl-containing amino acid, e.g. serine and threonine, with another; substitution of

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one acidic residue, e.g. glutamic acid or aspartic acid, with another; replacement of one amide-containing residue, e.g. asparagine and glutamine, with another; replacement of one aromatic, residue, e.g. phenylalanine and tyrosine, with another; replacement of one basic residue, e.g. lysine, arginine and histidine, with another; and replacement of one small amino acid, e.g., alanine, serine, threonine, methionine, and glycine, with another.

The alterations are designed not to abolish the immunoreactivity of the variant protein with antibodies that bind to the reference protein. Guidance in determining which amino acid residues may be substituted, inserted or deleted without abolishing immunoreactivity of the variant protein with an antibody specific for the respective reference protein are found using computer programs well known in the art, for example, DNASTAR software.

The ADAMTS-N proteins also encompass fusion proteins comprising an ADAMTS-N protein and a tag, i.e., a second protein or one or more amino acids, preferably from about 2 to 65 amino acids, more preferably from about 34 to about 62 amino acids, which are added to the amino terminus of, the carboxy terminus of, or any point within 20 the amino acid sequence of an ADAMTS-N protein, or a variant of such protein. Typically, such additions are made to stabilize the resulting fusion protein or to simplify purification of an expressed recombinant form of the corresponding ADAMTS-N protein or variant of such protein. Such tags are known in the art. Representative 25 examples of such tags include sequences which encode a series of histidine residues, the epitope tag FLAG, the Herpes simplex glycoprotein D, beta-galactosidase, maltose binding protein, or glutathione S-transferase.

The ADAMTS-N proteins also encompass ADAMTS-N proteins in which 30 one or more amino acids, preferably no more than 10 amino acids, in

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the respective ADAMTS-N protein are altered by posttranslation processes or synthetic methods. Examples of such modifications include, but are not limited to, acetylation, amidation, ADP-ribosylation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or a lipid, cross-linking gamma-carboxylation, glycosylation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, sulfation, and transfer-RNA mediated additions of amino acids to proteins such as arginylation and ubiquitination.

The ADAMTS-N proteins are immunogenic and, thus, are useful for preparing antibodies. Such antibodies are useful for identifying and diagnosing disorders which are associated with decreased expression or activity or increased expression of an ADAMTS-N protein. The 15 ADAMTS-N protein may also be useful for treating such disorder.

Diseases involving enhanced or depressed proteolyisis of the core proteins of the extracellular may involve enhanced expression or activity or decreased expression or activity of one or more ADAMTS-N proteins. Thus, ADAMTS-N proteins may be used to identify drugs,

20 polypeptides, auto-antibodies, or other natural compounds which bind to an ADAMTS-N protein with sufficient affinity to block or facilitate its activity. The activity of the ADAMTS-N protein is assayed in the presence and the absence of the putative inhibitor or facilitator using any of a variety of protease assays known in the

25 art. In general, the activity of the ADAMTS-N protein is assayed through the use of a peptide or protein substrate having a known or putative cleavage site for the ADAMTS-N protein. To detect cleavage or to monitor the extent of cleavage, the substrate is tagged in a manner which provides a detectable signal upon cleavage. For

side of the cleavage site and with a fluorescence-quenching group on the opposite side of the cleavage site. Upon cleavage by the substrate, quenching is eliminated and a detectable signal is produced. Alternatively, the substrate is tagged with a colorimetric leaving group that more strongly absorbs upon cleavage. Agents which block ADAMTS-N-catalyzed cleavage of a protein substrate may be administered to a subject to block proteolysis of the corresponding protein substrate.

#### ADAMTS-R1 Protein

- The present invention also relates to a protein, referred to hereinafter as "ADAMTS-R1". From its amino to its carboxyl terminus, ADAMTS-R1 comprises a signal peptide sequence, a TS1 module, a cysteine-rich domain, a spacer domain, and three TS1 modules. Thus, ADAMTS-R1 has a structure which is related to or similar to an
- 15 ADAMTS-N protein, but which lacks a catalytic domain and a disintegrin-like domain. In one embodiment, ADAMTS-R1, protein comprises amino acid 1 through amino acid 525 of the amino acid sequence, SEQ ID N0:22, shown in Fig. 11. Such protein has a 30-40% overall sequence identity with similar regions of the ADAMTS-N
- 20 proteins. The ADAMTS-R1 proteins also encompass variants of the amino acid sequence shown in Fig. 11 and fusion proteins which contain the amino acid sequence shown in Fig. 11 or a variant thereof. On the basis of its domain organization, it is expected that ADAMTS-R1 can bind to extracellular matrix or cell surface
- 25 molecules, including ADAMTS-N substrates. Thus, it is expected that ADAMTS-R1 can be used as an cell-matrix or cell-cell adhesion molecule or an ADAMTS-N competitive inhibitor. The ADAMTS-R1 proteins are also useful for preparing antibodies. Such antibodies are useful for identifying tissues where ADAMTS-R1 is expressed and 30 for diagnosing disorders which are associated with decreased

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expression or increased expression of. an ADAMTS-R1 protein.

#### Polynucleotides

The present invention also provides isolated polynucleotides which encode the mammalian ADAMTS-N proteins and the mammalian

- 5 ADAMTS-R1 protein. Figure 1 shows one embodiment of a polynucleotide, SEQ ID NO: 1, which encodes the full-length mouse ADAMTS-5 protein. Figure 2 shows one embodiment of a polynucleotide; SEQ ID NO: 3, which encodes a partial human ADAMTS-5 protein. Figure 3 shows one embodiment of a polynucleotide; SEQ ID NO: 5, which
- 10 encodes a full-length human ADAMTS-6 protein. Figure 4 shows one embodiment of a polynucleotide; SEQ ID NO: 7, which encodes a full-length human ADAMTS-7 protein. Figure 5 shows one embodiment of a polynucleotide; SEQ ID NO: 9, which encodes a full-length mouse ADAMTS-8 protein. Figure 6 shows one embodiment of a polynucleotide;
- 15 SEQ ID NO: 11, which encodes a partial human ADAMTS-8 protein.

  Figure 7 shows one embodiment of a polynucleotide; SEQ ID NO: 13,

  which encodes a full-length human ADAMTS-9 protein. Figure 8 shows

  one embodiment of a polynucleotide; SEQ ID NO: 15, which encodes a

  partial ADAMTS-9 protein. Figure 9 shows one embodiment of a
- 20 polynucleotide; SEQ ID NO: 17, which encodes a full-length human ADAMTS-10 protein. Figure 10 shows one embodiment of a polynucleotide; SEQ ID NO: 19, which encodes a partial mouse ADAMTS-10 protein. Figure 11 shows one embodiment of a polynucleotide; SEQ ID NO: 21, which encodes a full-length ADAMTS-R1 protein.
- Due to the known degeneracy of the genetic code wherein more than one codon can encode the same amino acid, a DNA sequence may vary from that shown in SEQ ID NO: 1 and still encode an ADAMTS-5 protein having the amino acid sequence of SEQ ID NO: 2. Similarly, a DNA sequence may vary from that shown in SEQ ID NO:5, and still sequence an ADAMTS-6 protein having the amino acid sequence set forth

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in SEQ ID NO:6. Similarly a DNA sequence may vary from that shown in SEQ ID NOS: 7, 9, 11, and 13, and still encode the amino acid sequences shown in SEQ ID NOS: 8, 10, 12, and 14, respectively.

Such variant DNA sequence may result from silent mutations, such as 5 for example those that occur during PCR amplification or from deliberate mutagenesis of a native sequence.

The present polynucleotides also encompass polynucleotides having sequences that are capable of hybridizing to the nucleotide sequences of FIGS 1 - 11 under stringent conditions, preferably 10 highly stringent conditions. Hybridization conditions are based on the melting temperature™ of the nucleic acid binding complex or probe, as described in Berger and Kimmel (1987) Guide to Molecular Cloning Techniques, Methods in Enzymology, vol 152, Academic Press. The term "stringent conditions, as used herein, is the "stringency" 15 which occurs within a range from about Tm-5 (5° below the melting temperature of the probe) to about 20° C below Tm. As used herein "highly stringent" conditions employ at least 0.2 x SSC buffer and at least 65° C. As recognized in the art, stringency conditions can be attained by varying a number of factors such as the length and 20 nature, i.e., DNA or RNA, of the probe; the length and nature of the target sequence, the concentration of the salts and other components, such as formamide, dextran sulfate, and polyethylene glycol, of the hybridization solution. All of these factors may be varied to generate conditions of stringency which are equivalent to the 25 conditions listed above.

The present polynucleotides also encompasses alleles of the ADAMTS-N and ADAMTS-R1 encoding sequences. As used herein, an allele or allelic sequence is an alternative form of an ADAMTS-N or ADAMTS-R1 encoding sequence which is present at the same gene locus. The 30 allele may result from one or more mutations in the ADAMTS-N or

ADAMTS-R1 encoding sequence. Such mutations typically arise from natural addition, deletion of substitution of nucleotides in the open reading frame sequences. Any gene which encodes an ADAMTS-N protein or ADAMTS-RI protein may have none, one, or several allelic forms.

5 Such alleles are identified using conventional techniques, such as for example screening, libraries with probes having sequences identical to or complementary with one or more ADAMTS-N polynucleotides.

The present polynucleotides also encompass altered

10 polynucleotides which encode ADAMTS-N proteins, ADAMTS-R1 proteins, and variants thereof. Such alterations include deletions, additions, or substitutions. Such alterations may produce a silent change and result in an ADAMTS-N protein having the same amino acid sequence as the ADAMTS-N protein encoded by the unaltered polynucleotide. Such 15 alterations may produce a nucleotide sequence possessing nonnaturally occurring codons. For example, codons preferred by a particular prokaryotic or eucaryotic host may be incorporated into the nucleotide sequences showing Figures 1 -11 to increase the rate of expression of the proteins encoded by such sequences. Such 20 alterations may also introduce new restriction sites into the sequence or result in the production of an ADAMTS-N or ADAMTS-RI variant. Typically, such alterations are accomplished using sitedirected mutagenesis.

The polynucleotides are useful for producing ADAMTS-N or

25 ADAMTS-R1 proteins. For example, an RNA molecule encoding an ADAMTSN protein is used in a cell-free translation systems to prepare such
protein. Alternatively, a DNA molecule encoding an ADAMTS-N protein
is introduced into an expression vector and used to transform cells.
Suitable expression vectors include for example chromosomal,

30 nonchromosomal and synthetic DNA sequences, e.g., derivatives of

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SV40, bacterial plasmids, phage DNAs; yeast plasmids, vectors derived from combinations of plasmids and phage DNAs, viral DNA such as vaccinia, adenovirus, fowl pox virus, pseudorabies, baculovirus, and retrovirus. The DNA sequence is introduced into the expression 5 vector by 5 conventional procedures.

Accordingly, the present invention also relates to recombinant constructs comprising one or more of the present polynucleotide sequences. Suitable constructs include, for example, vectors, such as a plasmid, phagemid, or viral vector, into which a sequence that, 10 encodes an ADAMTS-N protein or an ADAMTS-R1 protein has been inserted. In the expression vector, the DNA sequence which encodes the ADAMTS-N protein is operatively linked to an expression control sequence, i.e., a promoter, which directs mRNA synthesis. Representative examples of such promoters, include the LTR or SV40 15 promoter, the E. coli lac or trp, the phage lambda PL promoter and other promoters known to control expression of genes in prokaryotic or eukaryotic cells or in viruses. The promoter may also be the . natural promoter of the ADAMTS-N encoding sequence. The expression vector, preferably, also contains a ribosome binding site for 20 translation initiation and a transcription terminator. Preferably, the recombinant expression vectors also include an origin of replication and a selectable marker, such as for example, the ampicillin resistance gene of E. coli to permit selection of transformed cells, i.e. cells that are expressing the heterologous 25 DNA sequences. The polynucleotide sequence encoding the ADAMTS-N

protein is incorporated into the vector in frame with translation initiation and termination sequences.

The polynucleotides encoding an ADAMTS-N or ADAMTS-R1 protein

are used to express recombinant protein using techniques well known

30 in the art. Such techniques are described in Sambrook, J. et al

(1989) Molecular Cloning A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y. and Ausubel, F. M. et al. (1989) Cuurent Protocols in Molecular Biology, John Wile & Sons, New York, NY.

Polynucleotides encoding an ADAMTS-N or ADAMTS-R1 protein may

5 also be used for diagnostic purposes. The polynucleotides may be
used to detect and quantify ADAMTS-N or ADAMTS-R1 gene transcripts in
biopsied tissues in which enhanced expression or reduced expression
of the corresponding ADAMTS-N or ADAMTS-RI gene is correlated with a
disease. The diagnostic assay may be used to determine whether

10 expression is absent, present, or altered and to determine whether
certain therapeutic agents modulate expression of the corresponding
ADAMTS-N or ADAMTS-R1 gene.

Also encompassed by the present invention, are single stranded polynucleotides, hereinafter referred to as antisense

15 polynucleotides, having sequences which are complementary to the DNA and RNA sequences which encode the ADAMTS-N or ADAMTS-R1 proteins.

The term complementary as used herein refers to the natural binding of the polynucleotides under permissive salt and 5 temperature conditions by base pairing.

- The present invention also encompasses oligonucleotides that are used as primers in polyrnerase chain reaction (PCR) technologies to amplify transcripts of the genes which encode the ADAMTS-N and ADAMTSR-1 proteins or portions of such transcripts. Preferably, the primers comprise 18-30 nucleotides, more preferably 19-25
- 25 nucleotides. Preferably, the primers have a G+C content of 40% or greater. Such oligonucleotides are at least 98% complementary with a portion of the DNA strand, i.e., the sense strand, which encodes the respective ADAM-TS family protein or a portion of its corresponding antisense strand. Preferably, the primer has at least 99%
- 30 complementarity, more preferably 100% complementarity, with such

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sense strand or its corresponding antisense strand. Primers which are which have 100% complementarity with the antisense strand of a double-stranded DNA molecule which encodes an ADAMTS-N protein have a sequence which is identical to a sequence contained within the sense 5 strand. The identity of primers which are 15 nucleotides in length and have full complementarity with a portion of the antisense strand of a double-stranded DNA molecule which encodes the ADAMTS-N protein is determined using the nucleotide sequences, shown in FIG I - 11 and described by the general formula a-b; where a is any integer between 10 I and the position number of the nucleotide which is located 15 residues upstream of the 3' end of the sense or antisense strand of the cDNA sequences shown in FIG 1 -11; where b is equal to a+14; and where both a and b correspond to the positions of nucleotide residues of the cDNA sequences shown in FIGS 1 - 11.

- The present invention also encompasses oligonucleotides that are useful as hybridization probes for for isolating and identifying cDNA clones and genomic clones encoding the ADAMTS-N or ADAMTS-R1 protein or allelic forms thereof. Such hybridization probes are also useful for detecting transcripts of the genes which encode the 20 ADAMTS-N family proteins or for mapping of the genes which encode the ADAMTS-N proteins Preferably, such oligonucleotides comprise at least 210 nucleotides, more preferably at least 230, most preferably from about 210 to 280 nucleotides. Such hybridization probes have a sequence which is at least 90% complementary with a sequence 25 contained within the sense strand of a DNA molecule which encodes an ADAMTS-N protein or ADAMTS-R1 protein or with a sequence contained within its corresponding antisense strand. Such hybridization probes
- 30 within a range from about Tin 5'C (5'C below the melting temperature

"stringent conditions" as used herein is the binding which occurs

bind to the sense strand under stringent conditions. The term

Tm of the probe) to about 20°C to 25°C below Tm. The probes are used in Northern assays to detect transcripts of ADAMTS-N homologous genes and in Southern assays to detect ADAMTS-N homologous genes. The identity of probes which are 200 nucleotides 5 in length and have 5 full complementarity with a portion of the antisense strand of a double-stranded DNA molecule which encodes the ADAMTS-N protein is determined using the nucleotide sequences shown in FIG 1 - 10 and described by the general formula a-b; where a is any integer between I and the position number of the nucleotide which is located 200 .

10 residues upstream of the 3' end of the sense or antisense strand of the cDNA sequences shown in FIG 1 -10; b is equal to a +200; and where both a and b correspond to the positions of nucleotide residues of the cDNA sequences shown in FIG 1-10.

Such probes or primers are also useful for identifying tissues 15 or cells in which the corresponding ADAMTS-N or ADAMTS-R1 gene is preferentially expressed either constitutively or at particular state of tissue differentiation or development or in disease states. Expression of the ADAMTS-N or ADAMTS-R1 gene in a particular tissue or group of cells is determined using conventional procedures 20 including, but not limited to, Northern analysis, in situ hybridization to RNA or RT-PCR amplification. Isolated polynucleotides encoding an ADAMTS-N or ADAMTS-R1 protein are also useful as chromosome markers to map linked gene positions, to identify chromosomal aberrations such as translocations, inversions 25 and trisomies, to compare with endogenous DNA sequences in patients to identify potential genetic disorders, and as probes to hybridize and thus discover novel, related DNA sequences. For use in such studies and assays, the probes may be labeled with radioisotopes, fluorescent labels, or enzymatic labels. The assays include, but are 30 not limited to, Southern blot, in situ hybridization to DNA in cells

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and chromosomes, PCR, and allele specific hybridization.

#### Antibodies

In another aspect, the present invention relates to antibodies which are specific for and bind to the ADAMTS-5 protein, the ADAMTS-6 5 protein, the ADAMTS-7 protein, the ADAMTS-8 protein, the ADAMTS-9 protein, the ADAMTS-10 protein, or the ADAMTS-R1 protein. Such antibodies are useful research tools for identifying *tissues that contain elevated levels of the respective protein and for purifying the respective protein from cell or tissue extracts, medium of 10 cultured cells, or partially purified preparations of intracellular and extracellular proteins by affinity chromatography. Such antibodies are also useful for identifying and diagnosing diseases associated with elevated or reduced levels of an ADAMTS-N protein or ADAMTS-R1 protein. Such antibodies are also useful for monitoring 15 the effect of therapeutic agents on the synthesis and secretion of ADAMTS-N proteins by cells in vitro and in vivo. Such antibodies may also be employed in procedures, such as co-immunoprecipitation and co-affinity chromatography, for identifying other proteins, activators and inhibitors which bind to an ADAMTS-N or ADAMTS-R1 20 protein.

The present invention also provides a method for detecting an ADAMTS-N or ADAMTS-R1 protein, in a bodily sample from a patient using antibodies immunospecific for an ADAMTS-N or ADAMTS-R1 protein. The method comprises contacting the antibody with a sample taken from 25 the patient; and assaying for the formation of a complex between the antibody and the corresponding ADAMTS-N or ADAMTS-R1 protein present in the sample. The sample may be a tissue or a biological fluid, including but not limited to whole blood, serum, synovial fluid, stool, urine, cerebrospinal fluid, semen, diagnostic washes from 30 trachea, stomach and other bowel segments, tissue biopsies or excised

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tissue, cells obtained from swabs and smears. To monitor changes in expression of the ADAMTS-N protein during fetal development and pregnancy, it is preferred that the sample be amniotic fluid. To monitor changes in expression of the ADAMTS-N protein during joint 5 disorders, the preferred sample is synovial fluid. To monitor changes in expression of ADAMTS-N proteins during cancer, the preferred samples include, but are not limited to, serum, body fluids, or biopsy tissue. To monitor changes in expression of ADAMTS-N proteins during inflammation the preferred samples include, to but are not limited to, serum, body fluids, or biopsy tissue.

The sample may be untreated, or subjected to precipitation; fractionation, separation, or purification before combining with the anti-ADAMTS-N protein antibody. For ease of detection, it is

preferred that isolated proteins from the sample be attached to

15 a substrate such as. a column, plastic dish, matrix, or membrane,

preferably nitrocellulose. Preferably, the detection method employs

an enzyme-linked immunosorbent assay (ELISA) or a Western immunoblot

procedure.

Interactions between an ADAMTS-N protein in the sample and the corresponding anti ADAMTS-N antibody are detected by radiometric, colorimetric, or fluorometric means, size separation, or precipitation. Preferably, detection of the antibody-ADAMTS-N protein complex is by addition of a secondary antibody that is coupled to a detectable tag, such as for example, an enzyme, 25 fluorophore, or chromophore. Formation of the complex is indicative of the presence of the ADAMTS-N protein in the test sample. Thus, the method is used to determine whether there is a decrease or increase in the levels of the ADAMTS-N protein in a test sample as compared to levels of the ADAMTS-N protein in a control sample and to quantify the amount of the ADAMTS-N protein in the test sample.

Deviation between control and test values establishes the parameters for diagnosing the disease.

#### Preparing the ADAMTS-N proteins and the ADAMTS-R1 protein

The ADAMTS-N proteins and the ADAMT-SR1 protein may be produced 5 by conventional peptide synthesizers. The ADAMTS-N proteins and the ADAMTS-R1 protein may also be produced using cell-free translationsystems and RNA molecules derived from DNA constructs that encode an ADAMTS-N protein or an ADAMTS-RI protein. Alternatively, ADAMTS-N proteins are made by transfecting host cells with expression 10 vectors that comprise a DNA sequence that encodes the respective ADAMTS-N protein and then inducing expression of the protein in the host. cells. For recombinant production, recombinant constructs comprising one or more of the sequences which encode the ADAMTS-N protein or a variant thereof are introduced into host cells by 15 conventional methods such as calcium phosphate transfection, DEAE-dextran mediated transfection, transvection, microinjection, cationic lipid-mediated transfection, electroporation, transduction, scrape lading, ballistic introduction or infection.

The ADAMTS-N protein and the ADAMTS-R1 protein may be expressed 20 in suitable host cells, such as for example, mammalian cells, yeast, bacteria, insect cells or other cells under the control of appropriate promoters using conventional techniques. Suitable hosts include, but are not limited to, E. coli, P. pastoris, Cos cells and 293 HEK cells. Following transformation of the suitable host strain 25 and growth of the host strain to an appropriate cell density, the cells are harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract retained for further purification of the ADAMTS-N protein or the ADAMTS-R1 protein.

Conventional procedures for isolating recombinant proteins from 30 transformed host cells, such as isolation by initial extraction from

cell pellets or from cell culture medium, followed by salting-out, and one or more chromatography steps, including aqueous ion exchange chromatography, size exclusion chromatography steps, and high performance liquid chromatography (HPLC), and affinity chromatography may be used to isolate the recombinant ADAMTS-N protein or ADAMTS R1 protein

### Preparation of Antibodies

The ADAMTS-N proteins, and variants thereof are used as immunogens to produce antibodies immunospecific for one or more

10 ADAMTS-N protein. The term "immunospecific" means the antibodies have substantially greater affinity for one or more ADAMTS-N protein than for other proteins. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, and Fab fragments.

- Antibodies are also prepared using an oligopeptide having a sequence which is identical to a portion of the amino acid sequence of an ADAMTS-N protein. Preferably the oligopeptide has an amino acid sequence of at least five amino acids, and more preferably, at least 10 amino acids that are identical to a portion of the amino
- 20 acid sequence of an ADAMTS-N protein. Such peptides are conventionally fused with those of another protein such as keyhole limpet hemocyanin and antibody produced against the chimeric molecule. One preferred oligopeptide for preparing an antibody to mouse ADAMTS-5 has the sequence (C)HIKVRQFKAKDQTRF, SEQ ID NO: 30.
- 25 Another preferred oligopeptide for preparing an antibody to ADAMTS-5 is CEAKNGYQSDAKGVKTFVEWVPKYAG, SEQ ID NO: 3 1. One preferred oligopeptide for preparing an antibody to ADAMTS-6 has the sequence SVSIERFVETLVVADK(C), SEQ ID NO:23. One preferred oligopeptide for preparing an antibody to ADAMTS-7 has the sequence
- 30 (C) EVAEAANFLALRSEDPEKY, SEQ ID NO:24. One preferred oligopeptide for

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preparing an antibody to ADAMTS-8 has the sequence

CVKEDVENPKAVVDGDWGP, SEQ ID NO:25. One preferred oligopeptide for

preparing an antibody to ADAMTS-9 has the sequence

QHPFQNEDYRPRSASPSRTH, SEQ ID NO:26. Another preferred oligopeptide

for preparing an antibody to ADAMTS-9 has the sequence

PQNCKEVKRLKGASEDGEYF, SEQ ID NO:27. One preferred oligopeptide for

preparing an antibody for ADAMTS-R1 has the sequence QELEEGAAVSEEPS,

SEQ ID NO:28. Another preferred oligopeptide for preparing an

antibody for ADAMTS-R1 has the sequence YYPENIKPKPKLQE; SEQ ID NO:29.

10 Polyclonal antibodies are generated using conventional techniques by administering the ADAMTS-N protein or achimeric molecule to a host animal. Depending on the host species, various adjuvants may be used to increase immunological response. Among adjuvants used in humans, Bacilli Calmette-Guerin (BCG), and
15 Corynebacterium parvum. are especially preferable. Conventional protocols are also used to collect blood from the immunized animals and to isolate the serum and or the IgG fraction from the blood.

For preparation of monoclonal antibodies, conventional hybridoma techniques are used. Such antibodies are produced by 20 continuous cell lines in culture. Suitable techniques for preparing monoclonal antibodies include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV hybridoma technique.

Various immunoassays may be used for screening to identify
25 antibodies having the desired specificity. These include protocols
which. involve competitive binding or immunoradiometric assays and
typically involve the measurement of complex formation between the
respective ADAMTS-N protein and the antibody.

#### Polynucleotides that encode ADAMTS-N proteins

30 Polynucleotides comprising sequences encoding an ADAMTS-N

protein or an ADAMTS-R1 protein may be synthesized in whole or in part using chemical methods. Polynucleotides which encode an ADAMTS-N protein, particularly alleles of the genes which encode the ADAMTS-N protein, may be obtained by screening a genomic library or CDNA library with a probe comprising sequences identical or complementary to the sequences shown in Figures 1 - 10 or with antibodies immunospecific for a ADAMTS-N protein to identify clones containing such polynucleotide.

Example 1 ADAMTS-512 protein A cDNA encoding mouse ADAMTS-5 protein was obtained using IMAGE Clone 569515, purchased from Research Genetics, Huntsville, Alabama and 7 day old mouse embryo cDNA library from Clontech, Palo Alto, CA. A cDNA encoding human ADAMTS-5 protein was obtained using IMAGE Clone 345484 purchased from Research Genetics, Huntsville, Alabama 15 and a human fetal brain cDNA from Clontech. The clone inserts were sequenced in their entirety. Using oligonucleotide primers based on the sequences at the ends of the. clone inserts as template, successive rounds of RACE (Rapid Amplification of cDNA Ends) by PCR was performed at 5' and 3 ends. RACE primers were generated 50-200 20 bp from the ends of the sequences so that the contiguity of RACE clones with the I.M.A.G.E. clone could be clearly established. A single round of 5' and 3' 20 RACE sufficed for cloning of the entire coding sequence of the mouse ADAMTS-5 protein and part of the catalytic zinc binding site through to the stop codon of the human 25 ADAMTS-5 protein. Primers were designed with calculated Tm>72°C and RACE was performed with nested primers for each amplification. PCR used the Advantage PCR reagents (Clontech, Palo Alto, CA); the polymerase mix contained both Taq polymerase as well as proofreading polymerase to minimize PCR errors and employed "hot-start" PCR for 30 optimal efficiency. RACE used the following "touch-down" cycle

conditions; 95°C for 1 minute followed by 5 cycles of 95°C for 0.5
minutes, 72°C for 5 minutes, then 5 cycles of 95°C for 0.5 minutes,
70°C for 5 minutes and 20 cycles of 95°C for 0.5 minutes, 68°C for 5
minutes. The PCR products were analyzed by Southern blotting,
5 initially using [α³²P]-dCTP labeled.

Hybridizing bands were ligated into pGEM-T Easy (Promega,
Madison, WI) and individual clones were selected by another round of
Southern analysis. Automated nucleotide sequencing of both strands
of each clone were done at the Molecular Biotechnology Core of the .

10 Lerner Research Institute, Cleveland Clinic Foundation and nucleotide
sequence data were analyzed using the DNAStar software. By
integration of the overlapping sequences thus obtained, a contiguous
nucleotide sequence was determined. The nucleotide sequence of the
mouse ADAMTS-5 cDNA and the predicted amino acid sequence of the

15 protein encoded by this cDNA are shown in Fig. 1. The nucleotide
sequence of the human ADAMTS-5 cDNA and the predicted partial amino
acid sequence of the protein encoded by this cDNA are shown in Fig.
2.

The predicted molecular mass (Mr) of the mature ADAMTS-5

20 protein is 73717.50 daltons. It is expected that the actual Mr of the active ADAMTS-5 protein is different due to post-translational modification, which could potentially increase the Mr. The predicted domain organization of ADAMTS-5 protein relative to the cloned cDNA is shown in Figure 12. The pro-domain of the full-length mouse

25 ADAMTS-5 protein has 3 consensus cleavage signals for furin. The most carboxyl-terminal furin cleavage site in ADAMTS-5 predicts the processing site for generation of the mature protein The catalytic domain of the ADAMTS-5 protein contains eight cysteine residues and a reprolysin -zinc binding signature sequence, i.e., HEIGHLLGLSHD.

30 Five cysteine residues are upstream of the zinc binding sequence,

while three residues are downstream, an arrangement that is shared with other ADAMTS members. The zinc binding signature is followed by a "Met-turn". The catalytic domain is followed by a domain with 35% similarity to snake venom disintegrins. The disintegrin domain 5 contains eight cysteine residues. The first TS repeat contains 52 residues and is followed by a conserved cysteine-rich sequence termed the cysteine-rich domain, designated "CRD", to distinguish it from the cysteine-free spacer domain. The CRD contains ten conserved cysteines and demonstrates high sequence homology with the CRD of 10 other ADAMTS-N proteins. The spacer domain of mouse ADAMTS-5 is 158 amino acids in length and is followed by a second TS module. ADAMTS-5 contains three potential glycosylation sites in the mature protease one of which is just upstream of the start of the spacer domain and the second lies within the spacer domain and the third is near the 15 start of the disintegrin domain. The human ADAMTS-5 protein and the mouse ADAMTS-5 protein have 96% sequence identity. ADAMTS-5 bears 46% sequence identity to ADAMTS-4 (KIAA0688), which is characterized as being involved in catabolism of aggrecan core protein in arthritis and 60% identity to ADAMTS-1 which is involved in inflammation.

#### 20 Example 2 ADAMTS-6

The nucleotide sequence of a human cDNA encoding the fulllength ADAMTS-6 protein was obtained using IMAGE clone 742630, which
encodes EST AA400393, and a human fetal brain cDNA from Clontech.
RACE was performed as described above in Example 1. The I.M.A.G.E.

25 clone 742630 contained an ORF flanked by consensus splice sequences,
indicating the presence of introns. Two successive rounds of RACE at
the 5' end and a single round of RACE at the 3' end provided the
complete coding sequence of ADAMTS-6. The putative ATG codon is
within a Kozak consensus sequence and encodes the first methionine
30 within the ORF.

3. 3

The nucleotide sequence of the ADAMTS-6 DNA is shown in Fig. 3 The predicted amino acid sequence, SEQ ID NO:6, of the ADAMTS-6 protein is also shown in Fig. 3. The predicted Mr of the fulllength, unprocessed ADAMTS-6 protein is 97,115 daltons., and the 5 predicted Mr of the mature ADAMTS-6 protein is 68412.10 daltons. domain organization of the ADAMTS-6 protein is shown in Fig. 12. pro-domain of the full-length ADAMTS-6 protein has one consensus cleavage signal for furin. The catalytic domain of the ADAMTS-6 contains six cysteine residues and the reprolysin -zinc binding 10 signature sequence, HEIVHNFGMNHD, which is followed by a "Met-tum". The catalytic domain is followed by a domain with 35% similarity to disintegrins. The disintegrin domain contains snake venom eight cysteine residues. The first TS repeat contains 52 residues and is followed by a conserve CRD sequence which contains ten 15 conserved cysteines and demonstrates high sequence homology with the CRD of other ADAMTS proteins. The spacer domain of ADAMTS-6 is 127 amino acids in length and is followed by a second TS module. ADAMTS-6 contains four potential glycosylation sites within the pyo-domain and two in the mature protease one of which is in the cysteine rich 20 domain and the other of which is in the spacer domain. ADAMTS-6 bears 46% sequence identity to ADAMTS-1, which is involved in inflammation.

#### Example 3 ADAMTS-7.

The nucleotide sequence of a cDNA encoding an ADAMTS-7 protein

25 was obtained using IMAGE clone 272098, which encodes EST N4.8032, and
a human fetal brain cDNA from Clontech. RACE was performed as
described above in Example 1. The I.M.A.G.E. clone 272098 encoded a
putative pre-pro region and was extended in the 3'-direction by two
successive rounds of RACE. A typical signal peptide sequence lies

30 downstream of the first methionine in the translated ORF. This

methionine codon lies within a satisfactory Kozak consensus for translation initiation.

The nucleotide sequence of the ADAMTS-7 cDNA is shown in Fig. 4. The predicted amino acid sequence, SEQ ID NO: 8, of the ADAMTS-7 5 protein is also shown in Fig. 4. The predicted Mr of the hilllength, unprocessed ADAMTS-7 protein is 116,607 daltons, and the predicted Mr of the mature ADAMTS-7 protein is 84005 daltons. The domain organization of the ADAMTS-7 protein is shown in Fig. 12. The pro-domain of the full-length ADAMTS-7 protein has one consensus 10 cleavage signal for furin. The catalytic domain of the ADAMTS-7 protein contains eight cysteine residues and the reprolysin-zinc binding signature sequence, HELGHSFGIQHD, which is followed by a "Met-tum". The catalytic domain is followed by a domain with 30% similarity to snake venom disintegrins The disintegrin domain 15 contains eight cysteine residues. The first TS repeat contains 52 residues and is followed by a conserved CRD sequence which contains ten conserved cysteines. The spacer domain of ADAMTS-7 is 221 amino acids in length and is followed by a second TS module and a short sequence containing two cysteine residues. ADAMTS-7 contains three 20 potential glycosylation sites within the mature protease; one of which is just upstream of the spacer domain and one of which is within the spacer domain. ADAMTS-7 bears 35 % sequence identity to ADAMTS-1, which is characterized as being involved in inflammation and 32% identity to ADAMTS-2 which is a procollagen processing

#### Example 4: ADAMTS-8

25 enzyme.

The nucleotide sequence of a cDNA encoding a full-length, mouse ADAMTS-8 protein was obtained using IMAGE clone 1260693, which encodes EST AA855532, and a mouse embryo cDNA from Clonetech. The 30 nucleotide sequence of a cDNA encoding a partial ADAMTS-8 human

-30-

protein was obtained using IMAGE clone 2119838, which encodes EST A1400905, and a human fetal brain cDNA library from Clontech. RACE was performed, as described above in Example 1. The nucleotide sequence of the cDNA encoding the full-length ADAMTS-8 mouse protein and the amino acid sequence of such protein is shown in Fig. 5. The nucleotide sequence of the cDNA encoding the partial ADAMTS-8 human protein and the amino acid sequence of such protein is shown in Fig. 6.

The predicted Mr of the full-length, unprocessed ADAMTS-8 mouse 10 protein is 1260693 daltons, and the predicted Mr of the mature ADAMTS-8 protein is 68412.10 daltons. The pro domain of the fulllength ADAMTS-8 protein has one consensus cleavage signal for furin. The catalytic domain contains eight cysteine residues and the reprolysm-zinc binding signature sequence, HELGHVLSMPHD, which is 15 followed by a "Met-turn". The catalytic domain is followed by a domain with 20-30% similarity to snake venom disintegrins. The disintegrin-like domain contains eight cysteine residues. The first TS repeat is followed by a conserved CRD sequence which contains 10 conserved cysteines. The spacer domain of ADAMTS-8 is 146 amino 20 acids in length and is followed by a second TS module. The ADAMTS-8 protein contains 4 potential glycosylation sites within the mature protease: one is in the cysteine-rich domain; one is in the catalytic domain; and two are in the disintegrin-like domain. ADAMTS-8 bears 46% sequence identity to ADAMTS-1 and 42% identity to 25 ADAMTS-4.

#### Example 5: ADAMTS-9

The nucleotide sequence of a cDNA encoding a full-length, human ADAMTS-9 protein was obtained using IMAGE clone 646675, which encodes EST AA205581, and a human fetal brain cDNA from Clonetech. The 30 micleotide sequence of a cDNA encoding a partial ADAMTS-9 mouse

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protein was obtained using IMAGE clone 535663, which encodes EST AAl 06215, and a mouse cDNA library obtained from Clonetech. RACE was performed as described above in Example 1. The nucleotide sequence of the cDNA encoding the full-length ADAMTS-9 human proteinand the samino acid sequence of such protein is shown in Fig.6. The nucleotide sequence of the cDNA encoding the partial ADAMTS-9 mouse protein and the amino acid sequence of such protein is shown in Fig. 7.

The predicted Mr of the mature human ADAMTS-9 protein is

10 189777.20 daltons. The prodomain of the predicted ADAMTS-9 protein
has 3 consensus cleavage signal for furin. The catalytic domain of
the ADAMTS-9 contains eight cysteine residues and the reprolysin zinc binding signature sequence, HELGHVFNMPHD, which is followed by a
"Met-turn". The catalytic domain is followed by a domain with 25-30%
15 similarity to snake venom disintegrins The disintegrin domain
contains eight cysteine residues. The first TS repeat contains is
followed by a conserved CRD sequence which. contains 10 conserved
cysteines. The spacer domain of ADAMTS-9 is 124 amino acids in
length and is followed by 14 additional TS modules and a C-terminal
20 domain. The ADAMTS-9 protein contains 6 potential glycosylation
sites within the mature protease: one in the spacer domain, one in
TSP 1 -7, one in TSPI-8, and 3 in the C-terminal domain. The ADAMTS9 bears 44% sequence identity to ADAMTS-4.

Example 6: ADAMTS-10

The nucleotide sequence of a cDNA encoding a fall-length

ADAMTS- 10 protein was obtained using IMAGE clone 110403, which

encodes EST AA588434, and a human fetal brain cDNA from Clonetech.

The nucleotide sequence of a cDNA encoding a partial, mouse ADAMTS-10

protein was obtained using IMAGE clone 1077653, which encodes EST

30 AA822090, and a mouse embryo cDNA library from Clonetech. RACE was

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performed as described above in Example 1. The nucleotide sequence of the human ADAMTS-10 cDNA and the predicted amino acid sequence, SEQ ID 18, of the human ADAMTS-10 protein encoded by such DNA is shown in Fig. 9. The nucleotide sequence of the cDNA encoding the partial mouse ADAMTS-10 protein and the amino acid sequence of such protein is shown in Fig. 10.

The predicted Mr of the mature ADAMTS-10 protein is 95238 daltons. The pro-domain of the full-length ADAMTS-10 protein has no consensus cleavage signal for furin. The catalytic domain of the , 10 ADAMTS-10 contains eight cysteine residues and the reprolysin-zinc binding signature sequence, HEIGHTFGMNHD, which is followed by a "Met-turn". The catalytic domain is followed by a domain with 30% similarity to snake venom disintegrins. The disintegrin-like domain contains eight cysteine residues. The first TS repeat is followed by 15 a conserved CRD sequence which contains 8 conserved cysteines. The spacer domain of ADAMTS-10 is followed by 4 additional TS modules and a Kunitz domain. The ADAMTS-10 protein contains 2 potential glycosylation sites within the mature protease: one in the catalytic domain, and one in the TS 1-3 domain. ADAMTS-10 bears approximately 40% sequence identity to ADAM-TS1, which is characterized as being involved in inflammation.

#### Comparison of the ADAMTS-N Proteins.

As shown in Figure 11, the ADAMTS-5. ADAMTS-6, and ADAMTS-7 proteins share a common domain organization. From amino to carboxyl 25 termini, they are as follows:

1. A pre-pro region. A typical signal sequence of variable length is followed by a putative pro-region of variable length but demonstrating short stretches of sequence identity. Three cysteine residues are, predicted within each novel pro-domain, of which the
30 most C-terminal is an "asymmetric" cysteine lying within a sequence

context similar to the cysteine "switch" of the MMPs. All three novel cDNAs predict consensus cleavage signals for furin, three in the case of ADAMTS-5, and one each in the case of ADAMTS-6 and ADAMTS-7. The most carboxyl-terminal furin cleavage site in ADAMTS-5 predicts the processing site for generation of the mature protease. The amino terminus of the mature proteins is predicted to start at the residue immediately following the cleavage sites.

- 2. A catalytic domain. The catalytic domains are very similar to each other and contain eight cysteine residues and a typical
- 10 reprolysin-type zinc binding signature followed by a "Met-turn".

  Five cysteine residues are upstream of the zinc binding sequence,
  while three residues are downstream, an arrangement that is shared
  with other ADAMTS members. The methionine of the met-turn is not at
  a constant distance from the zinc-binding signature, but in all three
  15 novel proteases, a constant cysteine residue is present in that
  interval.
- 3. A disintegrin-like domain. The catalytic domain is followed by a domain of 60-90 residues with 35-45% similarity to snake venom disintegrins, but without the canonical cysteine arrangement seen in 20 the latter. This disintegrin-like domain is of comparable length in ADAMTS-5 and ADAMTS-7, it is considerably shorter in ADAMTS-6.
- 4. A TS module. The first TS repeat is very similar in all three novel proteases and very similar to the first TS repeat of other ADAMTSS. It contains the same number of residues (fifty-two) in all 25 three novel proteins.
  - 5. The cysteine-rich domain. This TS domain is followed by a conserved cysteine-rich sequence termed the cysteine-rich domain (CRD).
- 6. The spacer domain. This domain is of variable length, in all 30 ADAMTSs and lacks the sequence landmarks so characteristic of all the

other domains. It shows the least homology of all the domains.

7. A C-terminal TS module. The sequence of the second TS module is more variant between the members of the ADAMTS family than the first TS module, despite the conservation of the number and spacing 5 of cysteine residues.

Overall, the predicted mature forms of these proteases show 20-30% similarity to each other and to ADAMTS1-4 although this may be considerably higher or lower for individual domains as described above.

- ADAMTS-9 and ADAM-TS10 contain all the domains present in ADAMTS-5 through ADAMTS-8. In addition, ADAMTS-9 and ADAMTS-10 contain the following domains:
- A. ADAMTS-9: After the c-terminal TS1 domain which is present in ADAMTS5-8, ADAMTS-9 contains 13 additional and homologous 15 TS11 domains, thus, ADAMTS-9 contains a total of 15 TS1 domains, of which 14 are adjacent to each other in the c-terminal half of the molecule. The 15th TS1 domain from the N-terminus is followed by a unique c-terminal domain which does not possess recognizable domain structure and contains 196 residues including 9 cysteine residues.
- B. ADAMTS-10: After the c-terminal TS1 domain which is present in ADAMTS 8, ADAMTS-10 contains 3 additional and homologous TS1 domains, thus, that ADAMTS-10 contains a total of 5 TS1 domains, of which 4 are adjacent to each other in the c-terminal half of the molecule. The 5th TS 1 domain from the N-terminus is followed by an 25 additional 47 amino acid residues including six (6) cysteine
- residues. These 47 residues have sequence similarity of 30%-40% to the c-terminus of pro-hormone convertase 5 and 6, and to the Kunitz family of inhibitors.

#### Northern Analysis

Mouse embryo northern blots and multiple tissue northern blots

from human and mouse tissues (Clontech, Palo Alto, CA) were hybridized to the  $[\alpha^{32}P]$ -dCTP labeled inserts of I.M.A.G.E. clones as per the manufacturer's recommendations followed by autoradiographic exposure for 3-7 days.

In situ hybridization used cryosections of mouse embryos of gestational age 8.5 days and 10.5 days. Embryos were collected with the inclusion of the surrounding uterus and fixed overnight in 4% paraformaldehyde. Sense and anti-sense probes continuously labeled with digoxigenin-UTP (Boehringer-Mannheim, Indianapolis, IN) were 10 transcribed with T7 and T3 RNA polymerases, respectively, using as template a 63 0 bp EcoRI-Sacl fragment from the Adamts-5 clone 569515 (Fig. 14) cloned into pBluescript SK+ (Stratagene, La Jolla, CA). In situ hybridization was done essentially as previously described in Apte, et al. (1997) J. Biol. Chem. 272:2551-25517, which is 15 specifically incorporated herein by reference, except that sections were predigested with proteinase K (Boehringer-Mannheim, Indianapolis, IN) at a lower, concentration (1 -5  $\mu$ g/ml) than reported in Apte, et al.. Bound, digoxigenin-labeled probe was detected using an alkaline phosphatase tagged anti-digoxigenin 20 antibody (Boehringer-Mannheim, Indianapolis, IN) and nuclei were counterstained with methyl green.

Specific hybridization of the antisense Adamts-5 probe to sections of 8.5 day-old mouse embryos was obtained, whereas only low background staining was noted with the control sense probe. Staining 25 was uniform throughout the 8.5 day old embryos. In addition, there was labeling of mRNA in trophoblastic cells lining the uterine cavity as well as in the developing placenta (Fig. 14). The decidual reaction within the uterus also showed upregulation of Adamts-5 mRNA relative to the negative controls. In sections from 10.5 day old 30 embryos, labeling was widespread but less intense compared to the 8.5

day-old embryo. Labeled cells were seen in mesenchyme and somites as well as in the neural tube and developing hindgut. Northern analysis also indicated that mRNA encoding ADAMTS-5 was present in human placenta but was barely detectable in adult lung, heart, brain, 5 liver, skeletal muscle, kidney and pancreas.

Northern analysis showed undetectable expression of Adamts-6 during mouse embryo development. Northern analysis indicated that mRNA encoding ADAMTS-6 was present in human placenta but was barely detectable in adult lung, heart, brain, liver, skeletal 10 muscle, kidney and pancreas. Adamts-7 was expressed at low levels throughout mouse development. In adult human tissues examined with human cDNA probes, ADAMTS-7 mRNA was found in all tissues examined, i.e. in lung, heart, brain, liver, skeletal muscle, kidney, pancreas and placenta. The sizes of the mRNA species recognized by the probes 15 varied. ADAMTS-5 mRNA was approximately 10 kbp in size in human tissue. The most prominent Adamts-5 species was estimated at 7.5 kbp together with additional bands at 10 kbp and 4.5 kbp. The lone mRNA species detected by ADAMTS-6 probe was approximately 8.5 kbp, whereas the most common mRNA species detected by ADAMTS-7 probe 5 was 5 kbp 20 in size with an additional species seen at 7 kbp in skeletal muscle.

In mouse, ADAMTS-8 is expressed during fetal development (days 7, 11, 15, 17) and in adult mouse lung and heart with an mRNA size of approximately 3.8 kbp. In adult human tissue, ADAMTS-8 is expressed in lung and brain but not in heart, muscle, kidney, colon or thymus.

25 The mRNA size is 3.8 kbp.

ADAMTS-9 is expressed in lung, ovary placenta, heart, brain, muscle, kidney and pancreas with a mRNA size of 8 kb. In addition, kidney and ovary contain additional transcripts of size 3 kb and 4.4 kb respectively. These additional transcripts may represent

30 alternatively spliced or short forms of ADAMTS9.

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ADAMTS-10 is expressed in thymus, prostate, testis, ovary, small intestine, colon, peripheral blood leukocytes, heart, brain, placenta, lung, liver, muscle, kidney and pancreas, as well as in many cell lines such as A549, HeLa and K562. There are two 5 transcripts of 5 kb and 8kb present in all tissues.

#### Example 7: ADAMTS-R1

The nucleotide sequence of a cDNA encoding a full-length ADAMTS-R1 protein was obtained using IMAGE clone 752797 which encodes EST AA, and a human fetal brain cDNA from Clontech. RACE was 10 performed as described above in Example 1. The nucleotide sequence, SEQ ID NO:21, of the ADAMTS-R1 cDNA and the predicted amino acid sequence, SEQ ID NO:22, of the ADAMTS-R1 protein encoded by such DNA is shown in Fig. 11.

The predicted Mr of the full-length, unprocessed ADAMTS-R1 15 protein is 58358.20 daltons. The domain organization of the ADAMTS-10 protein is shown in Fig. 15. In contrast to the ADAMTS-N proteins of examples 1-6, ADAMTS-R1 protein does not have a prometalloprotease or disintegrin-like domain or a consensus cleavage signal for furin. ADAMTS-R1 has a signal (pre) peptide which is 20 followed by a first TS module and a conserved CRD sequence which contains 10 conserved cysteines. The spacer domain of ADAMTS-R1 is 115 amino acids in length and is followed by 3 additional TS modules and a short sequence of 33 amino acids. The ADAMTS-R1 protein contains one potential glycosylation sites which is in the spacer 25 domain. ADAMTS-R1 bears 30-40% sequence identity to ADAMTS1 and ADAMTS4 in the related domains. ADAMTS-R1 mRNA is present in human heart, brain, kidney, muscle, lung, placenta, testis, ovary, colon, intestine, and prostate. There are three transcripts of 2.5 kb, 4.7 kb and 6.5 kbp present in all such tissues. In mouse, expression is 30 seen in skeletal muscle, and the transcript size is 6.5 kb.

Although certain embodiments of this invention have been shown and described, various adaptations and modifications can be made without departing from the scope of the invention as defined in the appended claims.

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#### CLAIMS

- 1. An isolated mammalian protein selected from the group consisting of an ADAMTS-5 protein an ADAMTS-6 protein, an ADAMTS-7 protein, an ADAMTS-8 protein, an ADAMTS-9 protein, an ADAMTS-10 protein, and an ADAMTS-R1 protein.
- The isolated mammalian protein of claim 1 wherein said protein 2. comprises an amino acid sequence which is at least 95% identical to a sequence selected from the group consisting of: amino acid 262 through amino acid 930 of SEQ ID NO:2; amino , acid 1 through amino acid 518 of SEQ ID NO:4; amino acid 245 10 through amino acid 860 of SEQ ID NO:6; amino acid 233 through amino acid 997 of SEQ ID NO:8; amino acid 229 through amino acid 905 of SEQ ID NO:10; amino acid 1 through amino acid 245 of SEQ ID NO:12; amino acid 236 through amino acid 1882 of SEQ ID NO:14; amino acid 1 through amino acid 874 of SEQ ID NO:16; 15 amino acid 212 through amino acid 1081 of SEQ ID NO:18; amino acid 1 through amino acid 450 of SEQ ID NO:20; and amino acid 1 through amino acid 547 of SEQ ID NO:22.
- The isolated protein of claim 2 wherein said amino acid
   sequence further comprises a prepropeptide sequence at the amino terminus thereof.
  - 4. The isolated protein of claim 1 wherein said protein is a human ADAMTS-5 protein or a mouse ADAMTS-5 protein.
- 5. The isolated protein of claim 1 wherein said protein is a human25 ADAMTS-6 protein.
  - 6. The isolated protein of claim 1 wherein said protein is a human ADAMTS-7 protein.
  - 7. The isolated protein of claim 1 wherein said protein is a mouse ADAMTS-8 or a human ADAMTS-8 protein.
- 30 8. The isolated protein of claim 1 wherein said protein is a human

- ADAMTS-9 or a mouse ADAMTS-9 protein.
- 9. The isolated protein of claim 1 wherein said protein is a human ADAMTS-10 or a mouse ADAMTS-10 protein.
- 10. The isolated protein of claim 1 wherein said protein is a human ADAMTS-R1 protein.
- 11. An isolated polynucleotide comprising a sequence which encodes a mammalian protein selected from the group consisting of an ADAMTS-5 protein, an ADAMTS-6 protein, an ADAMTS-7 protein, an ADAMTS-8 protein, an ADAMTS-9 protein, an ADAMTS-10 protein, and an ADAMTS-R1 protein.
- 12. The isolated polynucleotide of claim 11 wherein said protein comprises an amino acid sequence which is at least 95% identical to a sequence selected from the group consisting of: amino acid 262 through amino acid 930 of SEQ ID NO:2; amino 15 acid 1 through amino acid 518 of SEQ ID NO:4; amino acid 245 through amino acid 860 of SEQ ID NO:6; amino acid 233 through amino acid 997 of SEQ ID NO:8; amino acid 229 through amino acid 905 of SEQ ID NO:10; amino acid 1 through amino acid 245 of SEQ ID NO:12; amino acid 236 through amino acid 1882 of SEQ 20 ID NO:14; amino acid 1 through amino acid 874 of SEQ ID NO:16; amino acid 212 through amino acid 1081 of SEQ ID NO:18; amino acid 1 through amino acid 450 of SEQ ID NO:20, and amino acid 1 through amino acid 547 of SEQ ID NO:22.
- 13. The isolated polynucleotide of claim 11 wherein said nucleotide
  25 sequence encodes a protein having a signal sequence at the
  amino terminus thereof.
  - 14. The isolated polynucleotide of claim 11 wherein said polynucleotide comprises a sequence selected from the group consisting of: nucleotide 800 through nucleotide 2810 of SEQ ID NO:1 of an allelic variant thereof; nucleotide 1 through

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nucleotide 1519 of SEQ ID NO:3 or an allelic variant thereof; nucleotide 754 through nucleotide 2602 of SEQ ID NO:5 or an allelic variant thereof; nucleotide 708 through nucleotide 3003 of SEQ ID NO:7 or an allelic variant thereof; nucleotide 962 through nucleotide 2992 of SEQ ID NO:9 or an allelic variant thereof; nucleotide 1 through nucleotide 739 of SEQ ID NO:11 or an allelic variant thereof; nucleotide 708 through nucleotide 5648 of SEQ ID NO:13 or an allelic variant thereof; nucleotide 1 through nucleotide 2625 of SEQ ID NO:15 or an allelic variant thereof; nucleotide 634 through nucleotide 3243 of SEQ ID NO:17 or an allelic variant thereof; nucleotide 1 through nucleotide 1642 of SEQ ID NO:19 or an allelic variant thereof; and nucleotide 51 through nucleotide 1625 of SEQ ID NO:21 or an allelic variant thereof.

- 15 15. The isolated polynucleotide of claim 11 wherein said polynucleotide hybridizes under stringent conditions to a nucleic acid molecule comprising a sequence complementary to the protein encoding sequence of SEQ ID NO:1; SEQ ID NO:3; SEQ ID NO:5; SEQ ID NO:7; SEQ ID NO:9; SEQ ID NO:11; SEQ ID NO:13; SEQ ID NO:15; SEQ ID NO:17; SEQ ID NO:19; or SEQ ID NO:21.
  - 16. An isolated polynucleotide having a sequence which is complementary to the protein encoding sequence of the polynucleotide of claim 11.
  - 17. An expression vector comprising a polynucleotide of claim 11.
- 25 18. A host cell transformed or transfected with an expression vector of claim 17.
  - 19. A method for producing an ADAMTS-N protein or an ADAMTS-R1 protein, said method comprising the steps of
- (a) culturing a host cell of claim 18 under conditions

  30 suitable for expression of an ADAMTS-N protein or an ADAMTS-R1

#### protein; and

- (b) recovering said ADAMTS-N protein or said ADAMTS-R1 protein from the host cell culture.
- 20. An antibody that binds to a protein selected from the group

  5 consisting of an ADAMTS-5 protein, an ADAMTS-6 protein, an

  ADAMTS-7 protein, an ADAMTS-8 protein, an ADAMTS-9 protein, an

  ADAMTS-10 protein and an ADAMTS-R1 protein.
  - 21. An oligopeptide for producing an antibody that binds to an ADAMTS-N protein or an ADAMTS-R1 protein wherein said
- oligopeptide has a sequence selected from the group consisting of:
  - a) SVSIERFVETLVVADK, SEQ ID NO:23;
  - b) EVAEAANFLALRSEDPDKY, SEQ ID NO:24;
  - c) VKEDVENPKAVVDGDWGP, SEQ ID NO:25;
- d) QHPFQNEDYRPRSASPSRTH, SEQ ID NO:26;
  - e) PQNCKEVKRLKGASEDGEYF, SEQ ID NO:27;
  - f) QELEEGAAVSEEPS, SEQ ID NO:28;
  - g) YYPENIKPKPKLQE; SEQ ID NO:29;
  - h) HIKVRQFKAKDQTRF; and
- 20 i) CEAKNGYQSDAKGVKTFVEWVPKYAG, SEQ ID NO:30.

Fig. 1

'MRLEWASLILILLLLSASCLSLAADSPAAAPAQDKTRQPQAAAA
AAEPDQPQGEETRERGHLQPLAGQRRSGLVHNIDQLYSGGKVGYLVYAGGRRFILD
LERDDTVGAAGSIVTAGGGLSASSGHRGHCFYRGTVDGSPRSLAVFDLCGGLDGFFAV
KHARYTLKPLLRGSWAEYERIYGDGSSRILHVYNREGFSFEALPPRASCETPASPSGP
QESPSVHSRSRRRSALAPQLLDHSAFSPSGNAGPQTWWRRRRSISRARQVELLLVAD
SSMARMYGRGLQHYLLTLASIANRLYSHASIENHIRLAVVKVVLTDKDTSLEVSKNA
ATTLKNFCKWQHQHNQLGDDHEEHYDAAILFTREDLCGHHSCDTLGMADVGTICSPER
SCAVTEDDGLHAAFTVAHEIGHLIGLSHDDSKFCEENFGTTEDKRLMSSILTSIDASK
PWSKCTSATITEFLDDGHGNCLLDLPRKQILGPEELPGQTYDATQQCNLTFGPEYSVC
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**SUBSTITUTE SHEET (RULE 26)** 

### Fig. 1 (con't)

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Fig. 2

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#### Fig. 3

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### Fig. 3 (con't)

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#### Fig. 4

**FEATURES** 

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### Fig. 4 (con't)

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  2881 eteccagete actgetggge caccaegggt ttggaagttt gettetetga geeteagtte
  2941 tocatctgtg agatgagget agegattgcc etgtgtccca ggcccgctgg gagggtacat
  3001 ggatgaggca ggtgggtgct ggctcgcggc gcatgttcag tgtgctccag ctcttggcgt
  3061 teteceteca ggggacacag etececeteg atagaccagt ecagtggece eteaceacac
  3121 tgacttattt ccctaaacta tttataaaaa gtagggcaat ttcattaact ctgactctta
  3181 cctgcccggg cggccgctcg agccgagtaa tcactagt
```

Fig. 5A

10	20	30	40	50	· <b>60</b>	70	
سيبلسيلسب	بليسانتينا	ليسلس	لتبيلينيا	لتبيلين	لنسلسنا		
tagggcgactgcac	qqqacqccqcqq	raggacgcgc	actcacaacc	cadadedece	atacteaaat	teta 70	
ctaggttggctggc							
gccgctagccgagt			·-				
gccaccagcacctg			•			_ <del>_</del>	
CTCCGCGACCCCAC							
360	370	380	390	400	410 .	420	
سيلسلس	بليستليسنا	لسباب	لتبيليب	البيطنيين	ليسلبب	<u> </u>	
TOGICTGCGGAGCC	000000000000000000000000000000000000000	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	GCGCAGGCCI	CCGACCTAGTC	GIGCCCACGC	CGTT 420	
GCCCGGCAGCGCGAG							
CCTGACGCCAGCTT	CTGGCGCCCGG	ATTCAAGAT	CGAGCGCCTC	GGGGGCTCGAC	30000000000	DGGGG 560	
GCGAGCCGGGACTG	CGTCCCTCCTTC	TTCTCTGGC	ACAGTGAATG	GAGAACGGGAC	FICECTGGCG	3CGAT 630	
GAGCIGIGICGCGG	CTCGAGCGGCT	CGITCTTCC	TGCCAGGCGA	GGAGTTCACC	ATCCAGCCAC	AGGCC 700	
710	720	730	740	750	760	770	
<del>mulmulm.</del>	بالبينانييا	لتتتبليين	لتتباليين	ليسليس	التنظينيا		
GCIGGGGACICCCI	GGACCAGCCTC	ATCGCCTGCA	CCCTCCCCC	CCGGGACAGO	CCCCCGAAGA(	0000G 770	
GCCICCCICCCCCCC	GAAGITTTCCCC	CICCCICAA	GGACTGGAGT	GGGAGGTGGA	TAATEEOTAE	3333CA 840	
GGGACAGGAGAGAA	GTGACAACGAA	BAGGACAGGA	AGCAGGACAA	CGACCCTTC	CTCAAAGAGA	CAGAA 910	
GACTCCCGCAAAGT	GCCACCACCCT	rcccairccaa	AACTAGAAGC	'AAGAGGITITG	IGICCGAGGC	TCGCT 980	
TCGTGGAAACACTT	CTGGTGGCTGA:	recerce are	CCTCCCTTCT	ATCCGACCGA	CTCCAGAAO	CACAT 1050	
1060	1070	1080	1090	1100 .	1110	1120	
سيلسيلنس	ليبيلينيا	لتسليب	لتتبليبنا	لتسلسي	لتسليب	<u> </u>	
CCTCACGGTGATGT	CAATGGCAGCC	CAATCTACA	AGCACCCGAG	CATCAGGAAC	ICCGICAACC	TIGIG 1120	
GIGGIGAAAGIGCI	AATAGTGGAAA	AAGAAAGATG	GGGCCCGGAA	GTGTCCGACA	ACGGGGGGCI	CACAC 1190	
TGCGCAACTTCTGC	AGCTGGCAACG	CGITTCAAC	AAGCCCAGTC	ACCGCCACCO	GGAGCACIAT	GACAC 1260	
TGCCATCTTGTTCA	.CCAGACAGAAC	TTCTGTGGGA	AGGGAGAGCA	GTGTGACACC	CIGGGGAIGG	CAGAC 1330	
GITGGCACCATCIC							
1410	1420	1430	1440	1450	1460	1470	
سيلستس	لتتتليبينا	لتتبيليين	لتسطيين	لتتتبليتينا	لتسليين		
CCCTGGCCCATGAG	CTAGGGCACGT	TCTCAGCATO	CCCCATGAT(	EATTCTAAGCC	CIGIGIGAGA	TIGIT 1470	
TGGGCCCATGGGCA	AGIACCACATG	ATGGCGCCAT	TCTTCATCC	ACCIGAACAAC	ACGCIGCCCI	GGICT 1540	
CCCTCCAGTCCTGTCTACCTCACAGACCTCCTGCATGATGGTCACGCAGATTGTCTTCTGCATGCCCCCA 1610							
CCTCGGTTCTGCCCCTCCCCACAGGCCTCCCGGGCCACAGCACCCTCTACGAGCTGGACCAGCAGTGCAA 1680							
GCAGATCTTTGGGC	CTGATTTCCGA	CACTGCCCC	AACACCICIG	TOGAGGACATO	TGTGTCCAGC	CICIGI 1750	

Fig. 5A (con't)

1760	1770	1780	1790	1800	1810	1820
سيلسيلسن						
GCCCGTCATCGGGAT						
CACCCTGTGGCCCTG	GGCACCIGIG	CCIGGAIGGI	AGCTGTGTAC	TCAAGGAGGA	TGTGGAGAAT	CCCAA 1890
GCTGTGGTAGATGG	AGACTGGGGT	CCCTGGAGAC	CCTGGGGACA	ATGITCICGC	ACCIGIGGIG	GAGGG 1960
ATACAATTCTCGAAC	CGIGAAIGIG	ATAATCCAAT	GCCTCAGAAI	CCACCAAGAT	TTTGCCTGGG	TGAAA 2030
CACTCAACTACCAAT	CATGCAACAC	AGAGGAAIGI	CCACCAAACC	<b>GAAAAAGCTT</b>	CCGGGAGCAG	CAGTG 2100
2110	2120	2130	2140	2150	2160	2170
	لتتبليين	ليتبليين	ليتبلينيا	لتستلسب	لتستلسب	
TGAGAAATATAATGC	CTACAACCAC	ACTGACCTGG	ATCCCAATTI	CCTGCAGTGG	GTCCCCAAGT	ATTCA 2170
GCAGTGTCCCCCGA(						
AAGCTAAGGTGATCG	ATGGCACTCT	<u>ergrácycce</u>	GATACICIGI	CCATCTGCGT	CCGGGGGCAA	TGTGT 2310
TAAGGCTGGCTGTGA	CATGIGGIG	AACTCACCIA	AGAAGCTGGA	CAAATGTGGG	GIGIGIGGG	GCAAA 2380
CCCACTCCCTGTAGG	AAGATCTCCC	CACITICATIE	CCCCTTCAGI	TATECTACA	ATGACATIGI	CACCA 2450
2460	2470	2480	2490	2500	2510 [.]	2520
<u> سىلىسلىس</u>	استلست	ليبطيب	لتتبليين	لتسلبين	ليسلس	<u> </u>
TCCCAGCTGGTGCCA	CAAACATTGA	IGIGAAACAG	CGGAGTCACC	CAGGGTTCAG	GAACGACGGC	AGCTA 2520
CCTGGCGCTGAAGAC						
GACATCTTGGTGAAG						
TCCAGGCCCTGCCTG	AGCCICTIAC	AGTACAGCTO	CIGACIGIGI	CICCICACCI	CTTCCCTCCA	AAAGT 2730
CAGATATACCITCIT	IGICCCCAAT	GACATGGACT	TCAGCGTGCA	GAATAGCAAG	GAAAGAGCAA	CCACC 2800
2810	2820	2830	2840	2850	2860	2870
استبليسا						
AACATCATTCAGTCA						
GAGGIAGCIGGCAGC						
GCTCTGAAACCTGA						
tctcttaggcttatgg						
caagatggcacggcc						
3160	3170	3180	3190	3200	3210	3220
استاستاسيا				لسلسل		
agagaagagggtata			•			
agaagtcgggatagg						
tttgcaaaggactag						
aatctacctcacago						
agcaagctccatagg						
	-	•	_	-		_

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Fig. 5A (con't)

Fig. 5B

10	20	30	40 ·		•	
<u> سياسياسيا</u>	ليبيلين	<del>L</del>	لبيا	·		
MLRDPTTTGWPPLLL	LLLQLPPPPI	VCGAPAGPG:	rgaqas 40			
ELWPIRLPGSASEL	AFHLSAFGQC	FVLRLAPDAS	SFLAPE 80			
FKIERLGGSSAAAGG	EPGLRGCFFS	GIVNGERESI	AAMSC 120			
VAGWSGSFLLAGEEF	TTQPQGAGDS	LDQPHRLQRV	VGPGQR 160			
REDPGLAAAEVFPLP	OGLEWEVENC	NGQGQERSII	VEEDRK 200			•
210	220	230	240			-
سيبلسلسد	ليتبلينيا	سسلس	Lui	·		<u>•</u>
QDKEGLLKETEDSRK	VPPPFGSKTR	SKRFVSEARE	VETLL 240			
VADASMAAFYGIDLQ	VHILIVMSMA	arīvkhpsif	NSVNL 280			
VVVKVLIVEKERWGP	EVSDNGGLTL	RNFCSWORRE	NKPSD 320			
RHPEHYDTAILFTRQ	NFCGKGĐQCI	TLEMADVGTT	COPDK 360			
SCSVIKDEGLQAAYT	LAHELGHVLS	MPHDDSKPCV	RLFGP 400			•
410	420	430	440			
سيبلسيلسيا	لتستليب	لستبليين	لبييا			
MGKYHMMAPFFIHVN	KUTLPWSPCSA	VYLTELLDDX	HGDCL 440		•	
LDAPTSVLPLPTGLR	GHSTLYELDQ	QCKQIFGPDE	RHCPN 480			
TSVEDICVQLCARHR	DSDEPICHIK	NGSLLWADGI	FPCGPG 520		•	
HLCLDGSCVLKEDVE	NPKAVVDŒDW	GPWRPWGQCS	FRICEG 560			
GIQFSNRECDNEMPQ	VGGRFCLGEF	VKYQSCNIE	ECPPNG 600	•		
610	620	630	640			
استلسلسل	لتتتبليتي	ليبيليين	ــــــــــــــــــــــــــــــــــــــ			<del></del> -
KSFREQQCEKYNAYN	HEDLDGNFLC	WYPKYSGVSI	PRDRCK 640			•
LFCRARGRSEFKVFE	AKVIDGTLCC	PDTLSICVRO	9QCVKA 680			
GCDHVVNSPKKLDKO	GVCGGKGTAC	RKISGSFTPE	SYGYN 720			
DIVTIPAGATNIDVK	QRSHPGVRNI	GSYLALKIAI	GOYLL 760	]		•
NENLAISAIEQDILV	KGTTLKYSGS	MATLERLOS	QALPE 800	ļ		
810	820	830	840			
استاستاست	ليتتأثيب	<u> </u>	لىسا			
PLIVQLLIVSGEVFP	PKVRYTFFVE	NDMDFSVQNS	SKERAT 840			
TNIIQSLPSAEWVLG	DWSECPSTCF	RESWORRIVE	IRDPSG 880			
	<del></del>					•

Fig. 6A

10 30 CGAGGCAGAAGGCCCTAGCGAGCCGCCACCGCCCTGGG 40 GCCACGAGTAGGACCAAGCGGTTTGTGTCTGAGGGGGCGC 80 TICGIGGAGACGCIGCIGGIGGCCCATGCGICCATGCCIG 120 CCTTCTACGGGGCCGACCTGCAGAACCACATCCTGACGTT 160 AATGTCTGTGGCAGCCCGAATCTACAAGCACCCCAGCATC 200 220 230 AAGAATTCCATCAACCTGATGGTGGTAAAAGTGCTGATCG 240 TAGAAGATGAAAAATGGGGCCCAGAGGTGTCCGACAATGG 280 GGGGCTTACACTGCGTAACTTCTGCAACTGGCAGCGGCGT 320 TTCAACCAGCCCAGCGACCGCCACCCAGAGCACTACGACA 360 CGGCCATCCTCACCAGACAGAACTTCTGTGGGCAGGA 400 420 430 GCCCCTGTGTGACACCCTGCGTGTGCCAGACATCGCGACC 440 ATTTGTGACCCCAACAAAGCTGCTCCGTGATCGAGGATG 480 AGGGCTCCAGGCGCCCACACCCTGGCCCATGAACTAGG 520 GCACGTCCTCAGCATGCCCCACGACGACTCCAAGCCCTGC 560 ACACGCTCTTCGGGCCCATGGGCAAGCACCACGTGATGG 600 610 620 640 CACCGCIGITCGTCCACCTGAACCAGACGCTGCCCTGGTC 640 CCCCTGCAGCGCCATGTTCTCAGGCTGCCACCTGCAGGGG 680 TGGATCCATTICAAGTATTTATGCAAATGTGTCTCTGAAC 720 TAAAGIGIGATCTTATGCC 739

10 20 30 4C

RAEGASEPPPPICATSRIKHEVSEARFVETLLVADASMAA 40

FYGADLQNHILTIMSVAARIYKHPSIKNSINIMVVKVLIV 80

EDEKWGPEVSLNGGLILRNFCNWQRRFNQPSURHPEHYDT 120

AILLTRQNFCQQEGLCDTIGVADIGTICDENKSCSVIEDE 160

GLQAAHTLAHELGHVLSMPHDDSKPCTRLFGEMGKHWMA 200

210 220 230 240

PLFVHLNQTLFWSPCSAMFSQCHLQSWIHFKYLCKCVSEL 240

KCDLM 245

Fig. 6B

Fig. 7A

10 	. 20	30 	<u>4</u> 0	50	60	70
GAAGCACCATGCAGTT						
CAGCCCAGACGCCGCC		CAACTACAC	33116661661			IGGG 70
CTGACCGAATACCAAA						
ACTTCAAAAGAACGCC	ACGGAGCATTA	ACTOTOCCA	CTGACCCCTG			CTTC 280
CTCCTCTACCTCCTCC						
360	370	380	390	400	410	420
بينينانسانيين	بالتبالية	بلينيلي	بالبيبليين	بليستليب	<u></u>	
GCCAATGCCGGATTTA	TOGCTOCACTG	TTCACTGTC	ACCCTCCTTG	GGACGCCCGG	GGTGAATCAG	ACCA 420
AGITTTATTCCGAAGA	GGAAGCGGAAC	TAAAGCACT	GTTTCTACAA	AAGGCTATGT	CAATACCAAC	TCCG 490
AGCACACGGCCGTCAT	CAGCCTCTGCT	CAGGAATGA	ACACAAAAAI	AGGCACAGIA	AAGACAAGAA	GAAA 560
ACCAGAGCAAGAAAAT	GGGGAGAAAGG	ATTAACCIG	GCTGGTGACG	TAGCAGCATT	AAACAGCGGC	TTAG 630
CAACAGAGGCATTITC	TOCTTATOGTA	ATAAGACGG	ACAACACAAG	AGAAAAGAGG	ACCCACAGAA	GGAC 700
710	· 720	<b>730</b> .	740	750	760	770
بالسياسيانيين	سليسلين	بلتستليد	بليسليب	بليتيلين	بالتسليب	<u> </u>
AAAACGTTTTTTATCC	TATCCACGGTT	TGTAGAAGT	CITGGIGGIG	GCAGACAACA	GAATGGTTTC	ATAC 770
CATGGAGAAAACCTTC	AACACTATATT	TTAACTTTA	ATGICAATIG	TAGCCICTAT	CTATAAAGAC	CCAA 840
GIATIGGAAATTIAAT						
CATATCTTTTAATGCT						
ATCCATCATGATACTG	CIGITCICITA	ACAAGACAG	CATATCTGCA	GAGCTCACGA	CAAATGIGAT	ACCT 1050
1060	1070	1080	1090	1100	1110	1120
بليسلسيليسلي	سلسيلس	بلينيلي	بليسيليب	ىلىنىلىن	بليستليب	
TAGGCCTGGCTGAACT	GGGAACCATTT	GIGATOCCT	ATAGAAGCTG	TICTATIAGI	CAACATAGIC	GATT 1120
GAGTACAGCTTTTACG	ATCGCCCATGA	GCTGGGGCCA	IGIGITIAAC	ATOCCICATO	ATGACAACAA	CAAA 1190
TGIAAAGAAGAAGGAG	TTAAGAGTCCC	CAGCATGIC	ATGGCTCCAA	CACTGAACTT	CIACACCAAC	CCT 1260
GGATGTGGTCAAAGTG	TAGTCCAAAAT	ATATCACIG	AGITTTTAGA	CACTOGTTAT	GGCGAGIGIT	TGCT 1330
TAACGAACCTGAATCC	AGACCCTACCC	TTIGCCIGN	CCAACTGCCA	CCCATCCTTT	ACAACGIGAA:	TAAA 1400
1410	1420	1430	1440	1450	1460	1470
CAATGNGAATTGATTT						
GCAATAACGICAATGG	_					
CGAGCCTGGAAAGCAC						
TCCTGGGGAAGTTGGA						
GAGAGTGCAACAGACC	AGAACCAAAAA	ATOGTOGAA	aatacigigi	AGGACGTAGA	ATCAAATTTA	AGIC 1750

## Fig. 7A (con't)

		, 1770	1780	1790	1800	1810	1820
			AGAAGOGAGA				
			TCCCAATGIG				
			AGTGGCAGGGA				
			CAAATGATAT				
			CACACATAAA CACACATAAA				
GATCAT							
	2110	2120	2130 سلسسسلىس	2140	2150	2160	2170
							GIGC 2170
			AGTTTCTCAGG				
			ATGGAAACTTT				
			TOCGAGACTG				
			CCGTCCCAAA				
GCAAGA				2490	2500	2510	2520
	2460	2470	2480 ىلىنىلىن				
			GTTTACTGG				
ATTCC	ATT.T.C+A-MC=4/TX	MACCICAGO	ACTTGTTTGCA		ALTO ALTO CALL		ATCA 2590
			GACACATTAC				
			JGCCCAGIGI				
CAIGI	TO TO COO		JACTGAGAAGG	TTGATGATG	TTTTTCCAGC	AGCCATCCCA	AACC 2800
					2850	2860	2870
,	2810	2820	2830 ىلىپىلىپ	2840			
			GAATGTAACAC				
			AGAGGAGAAGG				
			GAAAGTTACCA				
			TIGGICACCIG				
CAMAT		CICHEND V VIII.	atagaatgigi	CACCACA		TATCTATGCAC	ACTT 3150
CALTI.						3210	3220
	3160	3170	3180	3190	3200		
المسلمات			بلبينايين	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		בארבוויבוויבאר	7023 3220
GICAG	CAGCCGGAAI	GIGCAICCIG	GCAGGCGGGTC	CCIGGIAL	7.51.67.47.51.61.6		אבער 3220 אבער 3290
ATACC	AGCTAAGAGC	AG IGAAATGC	ATCATTGGGAC AGGACTGTGAA	TIMIMIGIO	MATCOTANAMIC	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	3360
GUAGC	AACTAGACCA	ACTGATACCC	ACCAAGAACCC	יא האכרניים. די דייר האיז האי	TGTCGTCCTCC	TETRYYYAE	TCAGC 3430
AAACG	ALCALAAGCA	CATACAGIGC	ACCAAGAACCC AGATACCTCAC	TATIOGORALI.	TOTAL LICE		ACGAG 3500
CACIT	GIGGGAAAGG	LACCCCGAIG	WITH CETCAL	بريورريطيط	TONE TONE		

## Fig. 7A (con't)

3510	3520	3530	3540	0000	3560	3570	
				•			
AGTGCCTGTGCTACC							
AGGCCTTGGACTGGA							
CAACTACAGTGACCA							
TGTTCCATGTCACCA							
ACTATOGTOCCOGGA							
3860	3870 "	3880	3890	3900	3910	3920	
CTGGGGAGCATGTTC							
GGATACACCGCAAAC							
GTCCTCAGTGGGCTT							
GGTGGTCTGTCAGCG GATCGTGAGCAGTGT					-	<del></del> -	
		_					
4210	4220	4230	4240	4250	4260	4270	
سسلسسلسد							
GTICIGICICITGIC							
AGAAAGIGATTACIG							
AAATGGAAAGCTGGC							
GCTGTCAGATCGGAA							
ATGCGAATGCCAAGG	CCCACGGIGI	CCCCTTTACA	CTTGGAGGGC	AGAGGAATGG	CAAGAAIGCA	ACCAAG 4550	
4560	4570	4580	4590	4600	4610	4620	
ليسلسيليسا	لتبتيليتين	لسلسلسا	لتتبليب	لستلسب	لتتبليت		
ACCIGCGGCGAAGGC	TOCAGGIACO	GCAAGGIGGI	GIGIGIGGAT	GACAACAAAA	ACGAGGIGCA	JTGGGG 4620	
CACGCTGTGACGTGA	CCAAGCGGCC	GGTGCACCGT	GAAAGCTGIA	GITTGCAACC	CIGCGAGIAI	GICIG 4690	
GATCACAGGAGAATC	GICAGAGIGO	TCAGIGACCT	GIGGAAAAGG	CTACAAACAA	AGGCTTGTCT	CGIGC 4760	
AGCGAGATTTAÇACC	CCGAAAGAGA	ATTATGAATA	CAGCTACCAA	ACCACCATCA	ACTGCCCAGG	CACGC 4830	
AGCCCCCCAGTGTTC	ACCCCIGITA	CCTGAGGGAG	<b>ICCCCIGICI</b>	CGGCCACCIG	CAGAGTTOGC	AACTG 4900	
4910	4920	4930	4940	4950	4960	4970	
ليسلسيلسيا	لتسلسب	لتتبايين	ليبتليين	لتتبليين	ليتبطينين	<del></del>	
GGGGAGCTGCTCAGT	GICTIGIGGI	GTTGGAGTGA	TGCAGAGATC	TGTGĊAATGt	ttaaccaatg	gaggac 4970	
caacccagccactta	tgccacactg	atctgaagcc	agaagaacga	aaaacctgcc	gtaatgtcta	taact 5040	
gtgagttaccccagaattgcaaggaggtaaaaagacttaaaggtgccagtgaagatggtgaatatttcct							
gatgattagaggaaagcttctgaagatattctgtgcggggatgcactctgaccaccccaaagagtacgtg							
acactggtgcatgga							

# Fig. 7Å (con't)

	5260	5270	5280	5290	5300	5310	5320
		ىلىسكى					
GICCCIAI	PAACGGGAG	CCCCCCATC	ACTGCCAATG	TCGGAAGGAI	TACACGGCCG	CIGGGITTIC	CAG 5320
TTTTCAG	AAATCAGA	ATAGACCTGAC	CAGCATGCAC	ATAATCACCA	CIGACTIACA	GTTTGCAAGG	ACA 5390
AGCGAAGC	ACATOCCG	rcccrrrrccc	ACAGCCGGGC	ATTCCTACAG	CCCTCCCAAG	TGCCCACAGG	GIC 5460
GTTTTAGC	ATCAACCT	MATGGAACCG	ECTTGTCTT	'AACIGAATCI	CCCAGATGGA	TATCACAAGG	GAA 5530
TIATGCTC	FICICIGAC	ATCAACAAGTC	CCCGGATGGI	ACCCGAGICG	TAGGGAAATG	CGGIGGITAC	TGT 5600
	5610	5620	5630	5640	5650	5660	5670
يتطيين	بليييلي	ببليتيايي	فيلتستليد	سلبنشي	سلينيلين	سلسسلند	
		CICIGGIACI					
AAGCCATT	ATGGATGG	ATGAAGGATAG	TAATGCAATA	LCCTCCACCTT	'AATTTGGGIG	CATGIGIATG	IGI 5740
GIGIGIGI	TIGIGIGI	CACTIGIATEC	TTGTGTGTGT	AAAIGIGIGI	ACATATACAT	ATATACA 58	04

Fig. 7B

10 خيراليسيانييا						70
<b>STARTITUTE</b>						
FKRIRRSINSAIDPW						
FYSEEEAELKHOFYK						
TEAFSAYGNKIDNIF						
IGNLINIVIVNLIVI	HNEQDGPSIS	<b>FNYOLLITKINE</b>	<b>CÓMÓH</b> ZN25C	GIHHDDAVLL	TRODICRAHD	KCDIL 350
360	370	380 .	े १९६८	400	410	420 -
ليسلسبلسي	لتسليب	لتتبليين	ليسلبين	لتتبيلتين	ليبتليين	ш
GLAELGTICDPYRSC	SISEDSGLST	AFTIAHELGH	VFNMPHDDNN	KCKEEGVKSP	QHVMAPILNF	YINPW 420
MWSKCSRKYTTEFLE						
NNVNGVHKGCRTQHI	PWADGIECEP	CKHCKXCFCV	PKEMDVPVII	GSWGSWSPFG	TCSRICGGGI	KTAIR 560
<b>ECNRPEPKNGGKYCV</b>	CRRMKFKSON	TEPCLKQKRD	FRDEQCAHFD	GKHFNINGLL	PNVRWVPKYS	GILMK 630
DRCKLFCRVAGVIAY	YQLRDRVIDG	TPCGQDINDI	CVQGLCRQAG	COHVLNSKAR	RDKCGVCGGD	NSSCK 700
710	720	730	740	750	760	770
ليسلسلس	لتشتلينين	لتتبليين	ليسلبين	ليسالين	ليستليب	
TVAGTENTVHYGYNT	VVRIPAGATN	IIDVRQHSFSG	ETODONYLAL	SSSKGEFLLN	GNEVVIMAKR	EIRIG 770
NAVVEYSGSETAVER						
CQGERKRKLVCTRES						
KYSRLDGKTEKVDDG					_	
DSKCIHQEKVTIQRO						
1060	1070	1080	. 1090	1100	1110	1120
استاستاست	لسسلسب	لسلسا	لستأسي	لىسىلىسى	لينتبليين	<u>l</u>
QQPECASWQAGPWVQ	CSVICGOGYO	LRAVKCIIGI	YMSVVDDNDC	NAAIRPIDIO	DCELPSCHPP	PAAPE 1120
TRRSTYSAPRICWRF						
ALDWSSCSVICGQGR						
YRPRSASPSRIHVLO						
PQWAYGWGECTKLC	=		=		-	
1410	1420	1430	1440	1450	1460	1470
ليسلسيلسن	لتسلبين	لتستليين	لتسلسن	ليبيانين	لستطيين	<u>l</u>
SVSCGRGHKQRIVYC	MAKDGSHLES	DYCKHLAKPH	CHRKCROGRO	PKWKAGAWSQ	CSVSCGRGVQ	QRHVG 1470 .
CQIGIHKIARETECN	PYTRPESECE	COGPRCPLYT	WRAEEWQECT	KICGEGSRYF	KVVCVDDNKN	EVHGA 1540
RCDVSKRPVDRESCS						
PPSVHPCYLRECPVS						
ELPQNCKEVKRLKG#	SEDGEYFLMI	RGKLLKIFCA	<b>GMHSDHPKEY</b>	VILVHGDSEN	IFSEVYGHRLH	NPTEC 1750

Fig. 7B (con't)

1760 1770 1780 1790 1800 1810 1820

PYNGSRRDDCQCRKDYTAAGFSSFQKTRIDLITSMQIITTDLQFARTSECHPVPFATAGDCYSAAKCPQGR 1820
FSINLYGTGLSLITESARWISQCNYAVSDLKKSPDGTRVVGKCGGYCGKCTPSSGTGLEVRVL.LRCFEEE 1890
AIMDG.RIVMQYLHINLGACVCVCVFVCDLYACVCKCVYTYIYT 1934

Fig. 8

OPF=2	
HIAVISLCSGMGTFRSHDGDYFTEPLQSVDÐQÐDERÐQN	40
KPHIIYRHSTPQREPSTGKHACATSELKNSHSKDKRKTRM	.80
PKRRKRNSLADDVALLKSGLATKVLSGYSNOINNIRDRWN	120
HKRIKEF LSYPREVEVMVVADHRMVLYHCANLQHYILIILM	160
SIVASIYKDSSIGNLINIVIVNLVVIHNEQEGPYINFNAQ	200
TTLKNFCQWQHSKNYLGGIQHDTAVLVTREDICRAQDKCD	240
TLGLAELGTICDPYRSCSISEDSGLSTAFTIAHELGHVFN	280
MPHDDSNKCKEEGVKSPQHVMAPTLNFYINFWMWSKCSRK	320
YTTEFLDTGYGECLI NEPASRTYPLPSQLPGLLYNVNKQC	360
ELIFGPGSQVCPYMMQCRRLWCNNVDGAHKGCRTQHTFWA	400
DGTECEPGKHCKFGFCVPKEMEGPAIDGSWGGWSHFGTCS	440
RTCGGGIKTAIREONRPEPKNGGKYCVGRRMKFKSCNTEP	480
CMKQKRDFREEQCAHFDGKHFNINGLLPSVRWFPKYSGIL	520
MKDRCKLFCRVAGNTAYYQLRDRVIDGTPCGQDINDICVQ	560
GLCRQAGCDHILNSKVRKDKCGICGGENSSCKIVAGIFNI	600
VHYGYNIVVRIPACATSIDVRQHSFSGKSEDDNYLALSNS	640
KGEFLLNGDFVVSMSKREVRVGSAVIEYSGSINVVERLNC	680
TDRIEEELLLQVLSVGKLYNPDVRYSFNIPIEDKPQQFYW	720
NSHGPWQACSKPCQGERRRKLVCTRESDQL/IVSDQRCDRL	760
PQPGPVTEACGIDCDLRWHVASKSECSAQCGLGYRILDIH	800
CAKYSRMDGKTEKVDDSFCSSQPRPSNQEKCSGBCSTGGW	840
RYSAWIECSRSCDOGIQRRRAICVNIRNDVLDDS 874	

Fig. 8 (con't)

•						
360	370	380	390	400	410	<u>42</u> 0
سيلسيلس	لتسليبيك	لىسلسى	لبيبليير	<del></del>	لسنبليب	
ACAGATGGAACCA	CAAAAGAACCAA	ACCCTTTCIC	TCCTACCCAC	GCTTGLAGA	GCCAIGGIG	GIGGC 420
TGACCACAGGATC	CTTTTATACCAC	GGAGCAAACC	TTCAACATTA	TATCITAACC	TIAAIGICCA	TIGIA 490
CCTTCTATCTATA	AAGACTCAAGTA	TTGGAAATTT	ITATAATTAA:	GITATIGIGA	actuagiigi	CATTC 560
ATAATGAACAGG	VAGGACCITACAI	AAATTTCAAI	GCCCAGACAA	CATTAAAGAA	CTTTTGCCAG	TGGCA 630
GCACTCAAAGAA	TACTICGGICGG	ATTCAGCACC	ACACAGCCGI	TCIGGICACA	AGGGAAGATA	TCTGC 700
710	720	730	740 -	750	760	770
سلسىلىيى	لتبيلينيك	لىسلىس	ليستلينين	لسيلسي	لبسلسيا	<del></del>
AGAGCTCAGGAC	VAATGTGACACCT	TAGGICTIC	TGAACTGGG	ACCATITGCG	ACCCCTACCG	AAGCT 770
GTTCCATTAGTG	AGACAGTGGGCT	GAGCACAGCI	TICACAATAC	CTCACGAGCT	GGGCCATGIG	TTTAA 840
TATGCCTCACGAT	GACAGCAATAAA	TOCAAAGAAC	AAGGAGTTA/	LCACTCCCCAG	CAIGICAIGG	CACCA 910
ACACTGAACTIC	PACACCAACCCCI	CGAIGIGGIC	CAAAGIGCAGI	CGGAAATACA	TCACIGAGII	CCIAG 980
ACACTGGGTACG	EAGAGTGCTTGCT	CAATGAACCI				
1060	1070	1080	1090	1100	1110	1120
سلسسسس	ليسلبين	لىسلىس	ليسلبينا	لتسليسا	<u></u>	
CGGCCTTCTCTAC	TAACGTGAATAA?	CAATGIGAAC	TGATTTTTG	GCCAGGCICI	CAAGIGIGCC	CCIAT 1120
AIGAIGCAGIGC	AGACGGCTCTGGT	CCAATAATG	rggatggagcz	ACACAAAGGCI	GCAGGACICA	AGCACA 1190
CGCCCTGGGCAG	ATGGAACCGAGTC	TGAGCCTGG	AAAGCACIGC	AGITIGGATI	TIGIGIICCC	AAAGA 1260
AATGGAGGGCCC	IGCAATTGATGG!	ATCCTGGGGA(	GTTGGAGCC	ACTITIGGGACC	TGCTCAAGAA	CGIGI. 1330
GGAGGAGGCATC	AAAACAGCCATCI	AGAGAGIGCA	ACAGACCAGA	CAAAAAAIU	GIGGGAAGL	
1410	1420	1430	1440	1450	1460	1470
سلىسلىس	سياسيان	سسلسب	سسلسسا	لسلسنا		
TAGGAAGGAGAA	TGAAGTTCAAAT	CIGCAACAO	3GAGCCCTGC	ATGAAGCAGAI	ACCGAGACTIC	CCACA 1470
GGAGCAGTGTGC	TCACTITGATGG	CAAACACTIC	AACATCAATG	CICICCIGCC	AGCGIACGC.	IGGITT 1540
CCTAAGTACAGC	GGAATTTTGATG	AAGGACCGGI	CAAGITGIT	CIGCAGAGIG	CAGGAAACAG	CAGCCT 1610
ACTACCAGCTCC	GAGACAGAGTGA:	MCACGGAAC	CCCTIGICGO	CAGGACACAA	AIGACAICIG.	IGICCA 1680
AGGCCTTTGCCG	GCAAGCTGGATG	IGATCATATT	TTAAACTCAA	AGGICCGGAA/	CATAAAIGI	
1760	1770	1780	1790	1800	1810	1820
سلسيست		<del>muliui</del>	ستبليبيا	سسلسب	بسلسب	
העטענבוובכוובות	בארע אוידי אוידע עי	AAAACAGTGG	CAGGAACATT	TAACACTGIO	CATTAIGGIL	ACAATA, 1820
ووعددستستسعو	عسكككسك	CTACCAGCAI	TGACGIGCGI	CAGCACAGCT	ICICAGGGAA	GICIGA 1890
CENTENCA ACTO	T	AAACAGTAAA	<i>G</i> GTGAATTCC	TGCTAAAIGG	ACACTITIGIT	GICICC 1360
רבת בבר ברודות	CACTICACIE	CCCACCCCC	TCATTGACTA	CACCGGATCG	GACAAIGIGG	MIGGAAA 2030
GACTGAACTGTA	CGCACCGIAICC	AGGAAGAACT	TCICCITCAC	GIGITGICCG	TGGGAAAGCT	GIATAA 2100

Fig. 8 (con't)

	2110	2120	2130	2140	2150	2160	2170
لسب	سسسسس	ببليسلين	بيلتنتيلين	بيلينيلين	سلسسلت	بالتسليب	<u>l.</u>
CCCAG	ATGTGCGGTACT	CATTCAATAT	TCCCATTGAG	GACAAACCTC	'AGCAATTITA	CTGGAACAGT	CAC 2170
CCCCCCC	FIGGCAAGCAIC	CAGCAAGCCC	TGCCAAGGG	AGCCGAGACC	AAAACTTGTT	TGCACCAGGG	AGT 2240
CTGAT	CAGCTAACCGT	TCTGATCAAA	GATGTGACCG	GCTGCCCCAG	CCAGGACCIG	TCACTGAAGC	GTG 2310
CCCCAC	CAGACTGTGACT	TGAGGTGGCA	CGTTGCCAGC	'AAGAGCGAAT	GCAGTGCCCA	GIGIGGITIG	GGC 2380
TACCG	TACTITAGACAT	CCACTGTGCC	'AAATACAGCA	GGATGGACGG	GAAGACGGAG	AAGGTGGATG	ACA 2450
	2460	2470			2500	2510	2520
للسلا	سيسيسين	سلسسلب	سلسسلت	<del>uluulu</del>	<del></del>	سلبسبليد	<u> </u>
GITTC	TGTAGCAGTCAA	LCCCAGACCGA	GTAACCAGGA	GAAATGCTCA	GGAGAGTGCA	GCACAGGTGG	ATG 2520
GCGCTZ	ATTCAGCCTGGA	CCGAAIGITC	TAGAAGCTGT	CATGGTGGTA	CCCAGAGAAG	AAGAGCAATT	TGT 2590
GTCAAC	CACCCGCAATGA	תבוניות הוביות	GACAGCAA 2	625			

Fig. 9A

						•	
	10.	. 20	30	40	50 	60	70
					GACCIATGAGA		
					CCCCCGAGCAC		· - · -
					ACCCACTTOCT		
_				•	CACGGGAGGG		
					GCCAGCAGCT		
	360	370	380	390	400	410	420
بيليين	-				ulluulu		
					EAGTACCTGAT		
					rggrgracaac		
GTCACCC	CCACCTGGAC	ACAGCCIGIC	CAGTGAGAGA	TGAGAAACC	TTGGAAAGGGC	CCCCATCCTC	SCT 560
GCGGACC	TTGÄAGCCAC	CCCCICCCAC	ACCCCTGGGG	AATGAAACAC	EAGCGTGGCCA	GCCAGGCCTC	AAG 630
CCATCCC	TCAGCCGAG	GCGCTACGTC	GAGACCCTGG	TIGGTGGCTG	ACAAGATGATG	GIGGCCIATC	ACG 700
	710	720 ·	730	740	750	760	770
بيلينيد	بالتبيلية	تلسيلت	نيليبيلين	بابيباب	بالبيانية	بالبياب	<u></u>
ccccccc	GGATGTOGAC	CAGTATGTCC	TGGCCATCAI	GAACATIGI.	ICCCAAACITI	TCCAGGACTC	GAG 770
TCTGGGZ	AGCACCGITIA	ACATCCICGI	AACTCGCCTC	ATCCTGCTC	ACGGAGGACCA	GCCCACTCTC	GAG 840
ATCACCC	ACCATGCCGC	GAAGICCCIA	GACAGCTICI	GLAAGIGGC	AGAAATCCATC	GTGAACCACA	.ccc 910
GCCATGC	CAATGCCATT	CCAGAGAACC	ETGTGGCTAA	CCATGACAC	AGCAGTGCTCA	ICACACGCIA	IGA 980
CATCTO	ATCTACAAGA	ACAAACCCTC	CCCCACACTA	.CCCCTCCCCC	1000000C4	ATGIGIGAGO	GCG 1050
	1060	1070	1080	1090	1100	1110	1120
بتلتيت	بالتستليب	بالبيبلين	بالتبيلين	بالبيبلية	تبليتيلين	بالتساليد	
AGAGAAC	CIGCAGCGIC	'AATGAGGACA	TTGGCTGCCA	CAAGCGITC	ACCATTGCCAC	GAGATOGGG	ACA 1120
CATTOGO	CATGAACCAI	GACGGGTGG	GAAACAGCTG	TEGGGCCCG	rggrcaggacc	CAGCCAAGCI	CAT 1190
GCTGCC	CACATTACCA	UTGAAGACCAA	CCCATTCGTC	TOGTCATCC	rocaaccgiga	CTACATCACC	AGC 1260
TITCTAC	ACTCCCCCI	CCCCCTCTCCC	CTGAACAACC	GGCCCCCAC	GACAGGACTTT	GIGUACCCGA	CAG 1330
TGGCACC	GGGCCAAGCC	TACGATGCAC	ATGAGCAATG	CCGCTTCAC	CATCGAGTCA	AATCGCGTCA	GTG 1400
	1410	1420	1430	1440	1450	1460	1470
بيليب	بالبيبلي	بيلتنياني	ببليسيلين	بلبيبلي	سلسلس	بطنتنكت	
TAAATAC	GGGGAGGTCT	CCAGCGAGCI	CICCICICIC	ACCAAGACC	AACCGGIGCAI	CACCAACAGC	ATC 1470
cccccccc	XCCGAGGGCAC	CCTGTGCCAC	ACGCACACCA	TCGACAAGC	GIGGIGCIAC	AAACGGGTCT	GIG 1540
					FIGGACICCAI		
					AGCCCCAGGCC		
AAGTACI	CICICOCIC	AGAGAAGGCCC	CACCGCTCCT	GCAACACGG	ATGACIGICCO	.0010001000	AGG 1750

## Fig. 9A (con't):

1760	1770	1780	1790	1800	1810	1820
ACTICAGAGAGTGC						
GTACCGGGGAGGGGG						-
AGGGCGCAGCCGTGC						
GCAAGCACGTGGGCTC				-		
TGACGGCAGTGCCTGC						
. 2110	2120	2130	2140	2150	2160	2170 -
<u> </u>						
GICGICIGGATICCCA	•					•
CCCTGAAGGGAGACCA						
TCTAGCTGGGACCACC	TTTCAACTGO	GACAGGGGCC	AGACCAGGIC	CAGAGCCTCG	AAGCCCTTGGGA	ACCG 2310
ATTAATGCATCTCTCA	TOGTCATOGT	GCIGGCCCGG	ACCGAGCTGCC	77600070006	CIACCOCTICA	ATG 2380
CCCCCATCGCCCGTGA	.CTCGCTGCCCO	CCCTACTCCTC	CACTATEC	SCCCTGGACC	AGIGCICOGC	CCA 2450 .
2460	2470	2480	2490	2500	2510	2520
بليبيليسليسي	بلينتلين	بالتسالية	بليسلين	بلنيبلي	بيلينياني	
GTGTGCAGGCGGTAGC	CAGGTGCAGG	CCCTCCACTCC	CGCAACCAG	TGGACAGCT	CCCCCCTCCCC	2520 -
CACTACTGCAGTGCCC	'ACAGCAAGCT	GCCCAAAAGGC	AGCGCGCCT	CAACACGGA	CCTTGCCCTC	CAG 2590
ACTOGGITGTAGGGAA	ETGGTCGCTC	TGCAGCCGCAC	CTGCGATGC	AGGCGTGCGC	AGTOGCTOGGI	CGT 2660
GTGCCAGCGCCGTC	TCTGCCGCGG	AGGAGAAGGCC	CTGGACGAC	AGCGCATGCC(	CCAGCCGCGC	CCA 2730
CCTGTACTGGAGGCCT	CCCYCOCCCO	CACTIGCCCIC	CCGGAGICGG	CAACCCTCGA	CIGGICIGÁGI	GIA 2800
2810	2820	2830	2840	2850	2860	2870
بلتيتلينينانينا	بلبيبلين	علىتتليين	سلسسلت	ىلىسىلىن	بيلينيناني	ــــــــــــــــــــــــــــــــــــــ
CCCCAAGCTGTGGGCC	TEGTCTCCCC	CACCGAGIGG	CCTTIGIAA	GAGIGCAGAIN	CAACGAICIAC	TCT 2870
GCCCCTGGGCACTGC	CTTCCTGCAG	CCAAGCCACC	ATCÌACIATG	CATGIAACI	receccectec	CCT 2940
CCICCCCCCICCGIC*	CCAGTGAGTQ	cccicyclel.	CCACACAGI	FIGGCCICGG	CAGCAGCAG	CCA 3010
CAGTGCGCTGCACCAC	CCACACCGGO	CAGCCATCICC	EAGAGTGCAC	IGAAGCCITG	COCCATOCAC	CAT 3080
GCAGCAGTGTGAGGCC	'AAGTGTGACA	GIGIGGIGCCC	CCTGGAGAT	3GCCCAGAAG	AATGCAAGGAT	GIG 3150
3160	3170	3180	3190	3200	3210	3220
بليبينلينينين	<u>ئاسىلىپ</u>	<u></u>	حلتينات	بليسلي	بالتسالين	
AACAAGGTGGCTTACT	GCCCCCTGGT	CCTCAAATTTC	CAGTICTGIA	CCCGAGCCTA	CTTCCGCCAG	YTGT 3220
GCTGCAAAACCTGCCA	AGGCCGCtag	ggtacctggaa	accaacctgg	agcacaggct	gaggcagggg	acat 3290
cccactggagagggca	ıtgagggaaag	<del>gggg</del> cttga:	attgaagggt	gagatgcagt	tgaaagttatt	tat 3360
tgggtaaccctacagg						
cttgcccagttgatag	jtgaagagaga	ggactccttg	tgcacacat	atttaagtcc	ctagcacccct	ccc 3500 ·

Fig. 9A (con't)

است	3510	3520	3530	3540 .	3550	3560	3570
accct	ttgatcggaat	atgtactgtg	agagtgggg	rggggaggg	gtgtgctggtg	jccctgcccc	stgc 3570"
actgt	tctatccctac	actetgagete	gggggattt	atatctgctat	tggggggagta	aggcttgatad	cac 3640
ctccci	tgtagccctcc	cccagactgad	cgaaggggaag	gatecacecca	acctctgcc	tgcctgccc	agg 3710
•		aggccgttcc					
caccaa	agaagccttac	attaaaaaagt	tgtgttatco	tacaaaaaa	aaaaaaaaact	cgagggggg	gccc 3850
	3860	3870	3880	3890	3900	3910	3920 🗸
بلبيين	بلينيليين	بليسانين	بالتسليب	علىبىلىن	بتلبينانين	بليبيلين	
antace	caattorooc	tatantaaatr	occintate 3	1885		•	•

Fig. 9B

_	10	20	30	40	
<del></del>		<del></del>		<u>uul</u>	
			AWTTTCHCWPS		
			FLLNLTRSSRL		
			HLQGQASSSHV		
			GSRSPEESGPH		
SSLRHPHLD	IACGVRI	DEKEWKGRP	WLRTLKPPPA	RFLON 200	
	10	220	230	240	
سسلسب	لسب	<del>b</del>	<del>Lundana</del>	uul	•
ETERGOPGLI	KRÞVSRE	RYVEILVV	ADKMMVAYHGR:	RDVDQ 240	
YVLAIMNIV	AKLFQDS	SLGSTVNII	VIRLILLTED	QPILE 280	
ITHHAGKSLI	DSFCKWC	KSTVNHSG	KNAIPENGVA	NHDTA 320	•
VLITRYDICI	CYKNKPC	CILGLARW	ADCVSAREAAA	SMRTL 360	
AATSVHHCHE	IGHIFC	MNHDGVEN	CGARGQDPAK	LMAAH 400	
41	LO	420	430	440	
ليستليبين	بلبيب	سيتليب	السلسا		
			IGLCINNRPP!		
			QCKYGEVCSEI		
			CWCYKRVCVPI		
			SSSRHCDSPRI		
			REVQCSEFDS		•
61		620	630	640	
			NEYTERAAAV		
			DLREDKCRVCC		
			KGSVHIFIQDI		
			LPLAGTTFQLF		
			PALRYRFNAPI		
81			•		
	-	820	830	840	•
		•	بلىسىلىسى		<del></del>
			AVECRNOLDSS		
			NVGNWSLCSRS		•
			POPRPPVLEAC		
			VLCKSADQRSI		
MULPAAKPPS	TWKCNI	KKCPPARW	TSEWGECSTQC	GLGQ 1000	

Fig. 9B (con't)

1010 1020 1030 1040

QRIVRCTSHIGQPSRECTEALRPSIMQQCEAKCDSVVPP 1040
GDGPEECKDVNKVAYCPLVLKFQFCSRAYFRQMCKICQG 1080
R 1081

SUBSTITUTE SHEET (RULE 26)

Fig. 10A

10 20 30 40	
multiplication of the second s	
ACCACCACCTGTGGTGGATGCAACACCCTGCCCCCTGAC 40	
ACCGICGACATTTGIGTCAGCCCGAGTCCAAGCATGIAG 80	
GCTGTGACAGGGTCCTGGGTTCTGATCTCCGAGAGGACAA 120	
ATOCCGIGIGIGIGGGGGGGGGGGGGGGGGGGGGGGGGGGG	
ATTGAAGGTGTCTTTAGCCCAGCTTTGCCAGGAACTGGGT 200	
210 220 230 2 <u>4</u> 0	
ATCAGGACGTCGTCTGGATCCCCAAAGGCTCGGTCCACAT 240	
TTTCATCCAAGATCTGAACCTGTCCCTGAGTCACCTGGCC 280	
CTANAGGGGGACCAAGAGTCTCTGCTACTGCAGGGGGTAC 320	
CTGGGACCCCCAACCTNACCGCCTTCCCCTGGNTGGGAC 360	
CACATITCATCTACGGCAGGGGCCGGACCAGGCACAGAGC 400	
410 420 430 440	.•
<u> </u>	
CIGGAAGCCCTGGGACCCATTAATGCATCTCTCATCATCA 440	
TGGTGCTGGCCCAGGCAGAGTTGCCTGCTCTCCACTACCG 480	
CTTCAATGCACCCATTGCCCGGCATGCACTGCCTCCCTAC 520	
TCCTGGCACTATGCCCCCTGGACCAAATGCTCAGCCCAGT 560	
GTGCAGGCGGCAGCCAAGTAGTGGAGTGCCGAAA 600	
610 620 630 640	
and	
TCAGCTGCACAGCTGAGCAGTGGCCCCACACTACTGTAGT 640	
GGCCACAGTAAATTGCCCAAGAGGCAGCGTGCCTGCAACA 680	
CAGAACCATGTCCACCAGATTGGGTTGTAGCAAACTGGTC 720	
ACCCTCCACCCGTACCTGTGACCCTCGTGTGCCGTACCCCC 760	
TCAGTGGTGTGCCAACGCCGGGTGTCTGCTGCAGAGGAAA 800	
810 820 830 840	
<u> </u>	
AAGCCITAGACGACAGTGCCTGTCCACAGCCACGCCCACC 840	
TGTGCTGGAGGCCTGCCAAGGCCCAATGTGCCCTCCTGAG 880	
TOOOCAACCCTCGACTGTCTCAGTGTACCCCAACCTGTG 920	
GCCCTGGTCTCCGCCACCGAGTGGTCCTTTGTAAGAGTGC 960	
AGATCAACGATCIACICIGCCCCCIGGGCACTGCCTTCCT 1000	

Fig. 10A (con't)

1010 1020 1030 1040	
	· · · · · · · · · · · · · · · · · · ·
GCAGCCAAGCCACCATCTACTATGCGATGTAACTTGCGCC 1	.040
GCTGCCCTCCTGCCCGCTGGGTGACCAGTGAGTGGGGTGA 1	.080
GIGITOCACACAGIGIGGCCTCGGCCAGCAGCAGCACCACA 1	120
GTGCGCTGCACCAGCCACACCGGCCAGCCATCTCGAGAGT 1	160
GCACTGAAGCCTTGCGGCCATCCACCATGCAGCAGTGTGA 1	200
1210 1220 1230 1240	
GCCCAAGIGICACAGIGIGGICCCCCCIGGAGATGGCCCA 1	240
GAAGAATGCAAGGATGTGAACAAGGTGGCTTACTGCCCCC 1	•
	320
CCAGATGIGCTGCAAAACCTGCCAAGGCCGCTAGGGTACC 1	
TGGAACCAACCTGGAGCACACGCTGAGGCAGGGGACATCC 1	400
1410 1420 1430 1440	
CACTEGAGAGGCCATGAGGCAAAGGCGGCCTTGAATTGAA	
GGGIGAGATGCAAGTTGAAAGTATTTATTTGGGTAACCCC 1	•
TACAGGGCTTCTGACTTAAGGGGTGGACAANAGCTGGCTA 1	•
CCCCAGGGACCCTTTGTTGGATCTTGGCCCANTTGATAG 1	
TGAAGAGAGACCTTCTTGGTGNACACATTTTTAAGTCC 1	.600
1610 1620 1630 1640	
- miliodio di maria d	:
TTAGACCCTTCCACCNTTGATCGCATATGTCTGGGAAGAG 1	.640
QN 1642	

Fig. 10B

	10	. 20	30	40
لسب	لبسلسب	بسابيين	استبأسيا	. ==
<b>AAAVV</b> I	GIPCRPDIV	DICVSGECK	IVGCDRVLGSD	LREDK 40
CRVCCC	DGSACETIE	GVFSPALPGI	GYEDVVWIPK	GSVHI 80
FIQDLA	ILSLSHLALK	GDQESLLLEC	LPGTPQPXRL	PLXGT 120
			IMVLAQAELP	
			QCAGGSQVQV	
	210	220	230	. 240
ىلىيىد	ليبيليي	ليسلس	ليساسي	<u> </u>
QLDSSA	VAPHYCSCH	SKLPKRQRAC	NTEPCPPDW	VCNWS 240
			EKALDDSACP	
			CGPGLRHRVVI	
DORSTL	PPGHCLPAAI	<b>OPSIMRONL</b>	RRCPPARWVI:	SEWGE 360
CSIQCG	LGQQQRIVR	TSHTGQPSR	ECTEALRPSTI	MOQCE 400
	410	420	430	440
ىلىبىد	لسبلب	ليبتليب	لسأسل	ші
AKCDSV	VPPGDGPEE	KDVNKVAYC	PLVLKFQFCSI	RAYFR 440
	COGR 450	•	-	

#### Fig. 11A

Ligated 459225+482392 with Sac I(168)&Eco RI(or Not I) Cloning site:5';Eco RI 3';Not I Vector; PT7T3 pac.

You can put this construct to pcDNA3.1(+) for transfection 5'-UTR is 50bp &3'-UTR is 175bp

210-215; in 482392 it's TCCTAC(SY).

			•			
	10 20	30	40 1 !			·
	gaattcggcacgaggcagtgtccgggatccaagcATGCAATGCTGCCC	TCGGGCAACT	ocitace 80 .			
	ACACTGCTCCTCTTTCTGGCTTTC GGACCGCACGCCCCACGAGGAGGACC TGCCTGGGGCCCCATGGAGTGAATC	COGREGOCT	ATGGGA 160			
	210 220	230 ىيىلىيىل	240 11		· · · · · · · · · · · · · · · · · · ·	
•	GGTGGGGCCGCCAACTCTCTGAG AGACCTGTGAAGGAAGAAATATC TAATGTGGACTGCCCACCAGAAG CAGCAATGCTCAGCTCA	GATACAGAAC CAGGICATTIC	ATGCAG 280 CGAGCT 320			
	AGITTIAIGAAIGGCITCCIGIG					
	410 420 	ستلسل	ــــــــــــــــــــــــــــــــــــــ			· · · ·
	CCCATGITCACTCAAGTGCCAAGGTGTGTTGAACTTAGCACCTAAGGTGCTATACAGAATCTTTGGATATGCCAAAATTGTTGGCTGCGATCACCAAAGAAGATAACTGTGGGGTCTG	CTPAGATOGIA TOCATCAGIOS AOCTOSGAAGO CAACOGAGATO	COCGIT 480 ATTIATG 520 ACCGIC 560 ACGICCA 600		·	
	610 620	630 سىلىسىل	640 	•		· .
	CCTGCCGGCTGGTCCGAGGGCAG CGCAACCAAATCGGATGATACTG GGAAGTAGACATATTCGCCTTGT ACTTATATCTGGAAACCAAAACC	TGETTGCAATT CTTAAAAGGT( CTCCAGGGGA(	CCCTAT 680 CTGATC 720 TTAAAGG 760			
	TGAAAACAGTCTCAGCTCCACAC	GAACITICCI	NGIGGAC 800			

### Fig. 11A (con't)

810 820 830 840	
	·
AATTCTAGTGTGCACTTCCACAAATTTCCACACAAAGAGA 840	
TACTGAGAATGGCTGCACCACTCACAGCAGATTTCATTGT 880	
CAAGATTCGTAACTCGCCCTCCGCTGACAGTACAGTCCAG 920	
TICATCTTCTATCAACCCATCATCCACCGATGGAGGGAGA 960	
CGCATTTCTTTCCTTGCTCAGCAACCTGTGGAGGAGGTTA 1000	• •
1010 1020 1030 1040	
and and and and and and and	
TCACCTGACATCGGCTGAGGCTACCATCTGAGGAGCAAC 1040	•
CGTGTGGTTGCTGACCAATACTGTCACTATTACCCACAGA 1080	
ACATCAAACCCAAGCTTCAGGAGTGCAACTTGGA 1120	
TCCTTGTCCAGCCAGTGACGCATACAAGCAGATCATGCCT 1160	•
TATGACCTCTACCATCCCCCTTCCTCGGTGGGACGCCACCC 1200	
1210 1220 1230 1240	
and make the desired and the second s	
CATGGACCGCGTGCTCCTCGTGTGGGGGGGGCATCCA 1240	
CACCCGGCCAGTTTCCTGTGTGCACGACGACCATCCAGGGG 1280	
CATGICACTICAGIGGAAGIGGAAATGCATGIACACCC 1320	
CTAAGATGCCCATCGCGCAGCCCTGCAACATTTTTGACTG 1360	
CCCTAAATGGCTGGCACAGGGTCTCCGTGCACAGTG 1400	
1410 1420 1430 1440	
ACGIGIGGCCAGGCCICAGATACCGIGIGGICCICIGCA 1440	•
TCCACCATCGAGGAGGCACACAGGAGGCTGTAGCCCAAA 1480	•
AACAAAGCCCCACATAAAAGAGGAATGCATCGTACCCACT 1520	
CCCTGCTATAAACCCAAAGAGAAACTTCCAGTCGAGGCCA 1560	
AGTIGCCATGGTTCAAACAAGCTCAAGAGCTAGAAGAAGG 1600	
1610 1620 1630 1640	
AGCTGCTGTCAGAGGAGCCCTCGTAAgttgtaaaagca 1640	
cagactgttctatatttgaaacttttgtttaaagaaagca 1680	
gtgtctcactggttgtagctttcatgggttctgaactaag 1720	
tgtaatcatctcaccaaagctttttggctctcaaattaaa 1760	
gattgattagtttcaaaaaaaaaaaaaagatgcggc 1800	

Fig. 11A (con't)

	1810	1820	1830	1840			
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фc	1803			•			

Fig. 11B

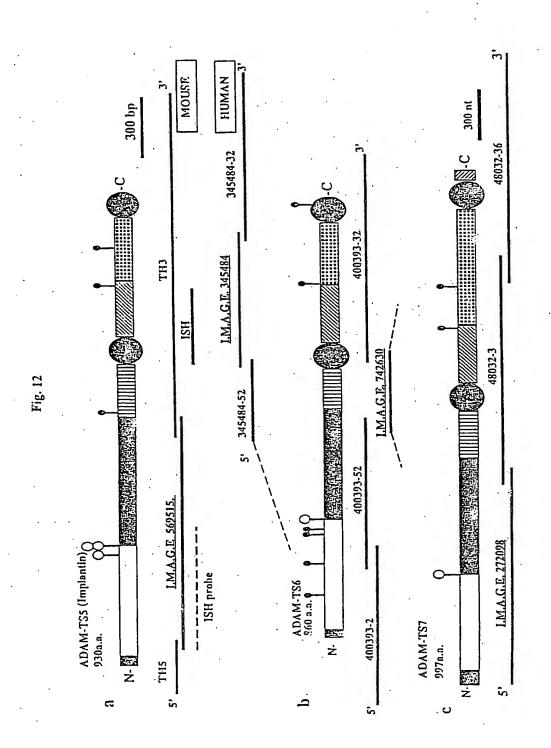
							_				
	Asp (D)	30	# cua	Leu(L)	3	# uca	Ser(S)	6	# gru	Val(V)	6
ugc	Cys (C)	26	# cuc	Leu(L)	11	# ucc	Ser(S)	10	#	Val(V)	29
ugu	Cys(C)	10	# cug	Leu(L)	14	# ucg	Ser(S)	5	# mm	???(X)	0
	Cys(C)	36	# cuu	Leu(L)	6	# ucu	Ser(S)	5	# TOT	AL	526
caa	Gln(Q)	7	# wua	Leu(L)	4	#	Ser(S)	43	#		

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10 20 30 40
<u> </u>
MECCRRATEGILLELAFLILSSRIARSEEDROGLWDAWG 40
FWSECSRICGOGAANSLRRCLSSKSCEGENIRYRICSNVD 80
CPPEAGDFRAQQCSAHNDVKHHGQFYEWLPVSNDPDNPCS 120
LKCQAKGITLVVELAPKVLDGIRCYTESLIMCISGLCQIV 160
GCDHQLGSTVKEINCGVCNGDGSTCRLVRGQYKSQLSATK 200
210 220 230 240
and
SDDTVVAIPYGSRHIRLVLKGPDHLYLETKTLQGTKGENS 240
LSSIGTFLVINSSVDFQKFPDKETLRMAGPLTADFTVKIR 280
NSGSADSTVQFTFYQPITHRWRETDFFPCSATCGGGYQLT 320
SAECYDLRSNRVVADQYCHYYPENIKPKPKLQECNLDPCP 360
ASDGYKQIMPYDLYHPLPRWEATPWIACSSSCGGIQSRA 400
410 420 430 440
and
VSCVEEDIQCHVTSVEENKCMYTPKMPIAQPCNIFDCPKW 440
LAQEWSPCTVTCGCGLRYRVVLCTDHRGMHTGGCSPKTKP 480
HIKEECIVPTPCYKPKEKLPVEAKLPWFKQAQELEECAAV 520

SEEPS. 526



**SUBSTITUTE SHEET (RULE 26)** 

a ·	
MRLEWASILLLILIL SASCISLAADSPAAAPAQDKTRQPQAAAAAAEPDQPCGEETREFGGIQPLAGORRSGGLVHNIDQ	20
LYSCOCKVGYLVYAGCRRFLLDLERDDIVGAAGSIVIAGGILSASSCHRGHCTYRGIVDGSPRSLAVFDLCGGIDGFFAV	160
KHARYTLKPILIPGSWAEYERIYGEGSSRII HVYNREGF SFEALPPRASCETPASPSGPQESPSVHSRSRRRSALAPQLID	240
HSAFSPSQUAGPQUWPRRRRSISRARQVELLLVADGSVARMYGRGLQHYLLTLASIANRLYSHASIENHIRLAVVKVVV	320
LIDKDISLEVSKVAATILKNECKOHOHOOLGIDHEEHYDAAILFTREDICGHES DILGMADVGITCSPERSCAVEED	400
GLHAAFTVÆHEIGHILGISHIDSKYCEENFGTTEIKRIMESILTSIDASKEWSKCTSATTTEFIDDGKKYCILTIJFRKQI GHILGISHIDSKYCEETFGSTEIKRIMESILTSIDASKEWSKCTSATTTEFIDGKKYCILTIJFRKQI   Dis	
LGPEELFGOTYDATQQCNLTFGFEYSVCFGMDVCARLWCAVVFQGMVCLTKKLPAVEGTFCGKGRVCTQGKCVDKTKKK LGPEELFGOTYDATQQCNLTFGFEYSVCFGXDVCARLWCAVVFQGMVCLTKKLPAVEGTFCGKGRLCLQGKCVDKTKKK	560
YYSTSSHQMGSWGRWGQCSRSCGGGVQFAYRHQWPAPRNSGRYCTGKRAIYRSCSVTRCPPNGKSFRHEQCEAKNGYQ YYSTSSHQMGSWGSWGQCSRSCGGGVQFAYRHQWPAPRNMGRYCTGKRAIYHSCSIMRCPPNGKSFRHEQCEAKNGYQ	640
SDAKGVKTFVEWFKYAGVLPADVČKLIČRAKGIGYYVVFSPKVIDGTEČRPYSNSVČVRGRČVRIGČDGI IGSKLQYDK SDAKGVKTFVEWPKYAGVLPADVCKLICRAKGIGYYVVFSPKVIDGTECRPYSNSVCVRGKCVRIGCDGI IGSKLQYDK  * *4 Spacer domain	
CGVCGCINSSCTKIIGIFNKKSKGYTDWRIPPGATHIIKVRQFKAKDQTRFPAYLALKKKTGEYLINGKYMISTSETTID CGVCGCINSSCTKIVGTFNKKSKGYTDWRIPPGATHIIKVRQFKAKDQTRFTAYLALKKKNGEYLINGKYMISTSETTID	
INGTVMYSGWSHRODFLHGYGYSATKETLIVQILATDPTKALGVRYSFFVPKKTTQKVNEVISHGAKVGPHSTQLQWV INGTVMYSGWSHRODFLHGYGYSATKETLIVQILATDPTKPLDVRYSFFVPKKSTFKVNEVTSHGAKVGSHTSQFQWV	880
TGFWLACSRICDIGWHIRIVOCODGWRKLAKGCILSORPSAFKOCILKKC TGFWLACSRICDIGWHIRIVCCODGWRKLAKGCIPLSORPSAFKOCILKKC	930

Fig. 13

D
MEILMKILIWILSLIMASSEFHSIJRISYSSQEEFLIYLEHYQLITPIRVIQAAFLSFIVANIKISKRRRSNDPIDPQQ 80

AVSKLEFKLSAYGREFIJALITLNIDFVSKHFIVEYWKADOPRINGHELDKÄYTGYLODPSTIKVALSAVVEJHSVIAT 160
EDEYY IEPLANTEDSKHFSYDAJERIVIYKKSALOQRILYZHSHGOSIFTRSGRWINDTSIVSYSLFINNIHHH 240

RQRGSVSIERFVEILWALKAMAGYHJRADLITHYDICTYRKGATGILG ASVAGAEPPRSCSINEDIGLGSAFT 400

RQRGSVSIERFVEILWALKAMAGYHJRADLITHYDICTYRKGATGILG ASVAGAEPPRSCSINEDIGLGSAFT 400

LUFETVHNEGSHTJEIGNSCGRKJAGONYGSSHYCEYQSFFLVCLQSPLHDLFREVORELMILSKSRCVINSIPAAE 480

LUFETVHNEGSHTJEIGNSCGRKJAGONYGSSHYCEYQSFFLVCLQSPLHDLFREVORELMILSKSRCVINSIPAAE 480

GILCOGNIENGAYYGALVFTGRYYMAGYTGGSVRCAINTLABGYNFYTERAPAVIIGTQOADSIDICTNEE 640

RHVCINILGSDAREIRCRAGGGSTGTAFEFFINGLIFRGYMEWQIPGSVHTEVREVARSAYTALKSEGDDYTI 720

NGAWTILWFRIGDVAGTAFHYKRPIDEFFSLFALGPTSENLIVMLLQEDALGIRYKFNVPITRIGSGINEVGFTWAHDP 800

CC

MCGCPSFFRSPAFLLRPILLILLCALAPGAPGPAFGRATEIGRALDIVHPVRVDAGGSFLSYELWFRAIRKRDVSVRRDAPA 80

EYELQYRGFELRPILTANQHILAPGAPGPAFGRATEIGRALDIVHPVRVDAGGSFLSYELWFRAIRKRDVSVRRDAPA 80

FYELQYRGFELRPILTANQHILAPGAPGPAFGRATEIGRALDIVHPVRVDAGGSFLSYELWFRAIRKRDVSVRRDAPA 80

EXWETLAWADAKWEYHOQPQVESYVLTTMAWAGLFHDPSIGNPHITTIVRIVLLEDEFELKITHHADNILSFGW 320

CKSINMAGDAHPLHHDTAILLTRKDLCAANARAGEILGLSVAGAGPHRSGSDEDIGJFAFTVFELGISFGIQHG 400

SGALCEPUGRPF TAPPQLLYDAAPLIVERGSRYTTRFLDRGMALCLDDPPRAGTILFFSVPFGVLYTVARQTELQFRQ
SGALCEPUGRPF TAPPQLLYDAAPLIVERGSRYTTRFLDRGMALCLDDPPRAGTILFFSVPFGVLYTVARQTELQFRA 480

YSAFCEIMMACDAHPLHDTAILLTRKDLCAANARAGEILGLSRVAGAGPHRSGSDEDIGJFAFTVFELGISFGIQHG 560

SGALCEPUGRPF TAPPQLLYDAAPLIVERGSRYTTRFLDRGMALCLDDPPRAGTILFFSVPFGVLYTVARQTELQFRA 560

AERCCTOPTPRYNGRYCVGGERRFFLOLLOACDAGRPSFRHWCSHTDMALYKGQLRIVWAVANDANGELARPANEYF 640

AKKRDAVUGGRRYGVASRDLCTIGGCNAGGGFERDSGAMEDRGCOVHAGGTGCHTANGTTEEABGLGVAVALLIPA 720

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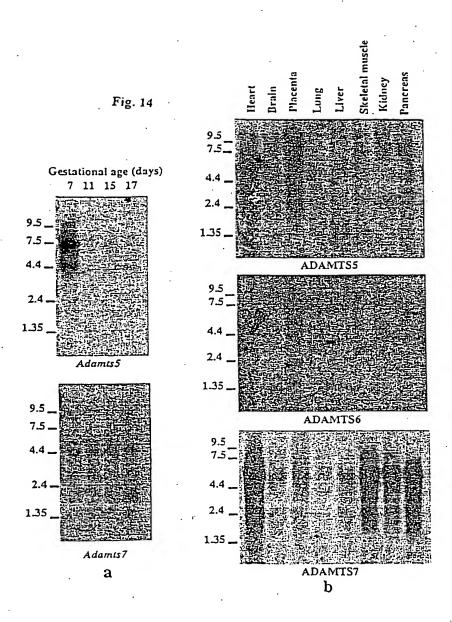
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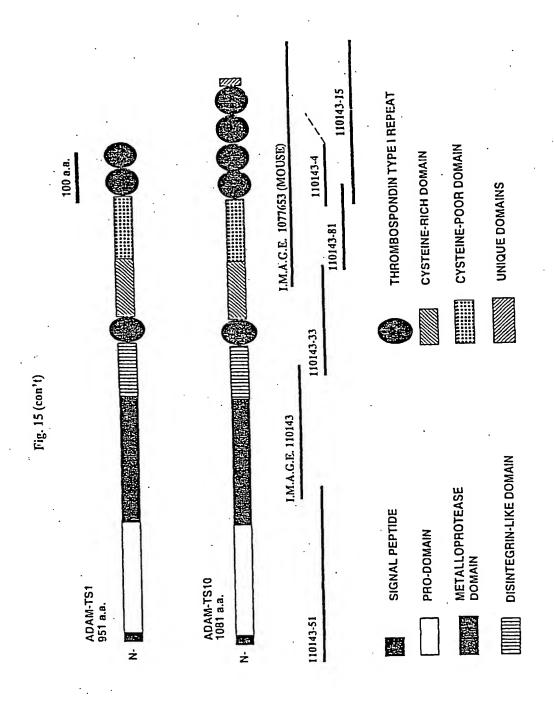
Fig. 13 (con't)

. CWATTGLEVCFSEPOFSICEMRLAIALCPPPAGRVHG 997

		adamalysin II atrolysin A	HELGHNLGME HD HELGHNLGMV HD	
	a	hADAM-9 hADAM-10 hADAM-15 hADAM-17 mADAM-19	HELGHNLGMNHD HEVGHNFGSPHD HELGHSLGLDHD HELGHNFGAEHD HEIGHNFGMSHD	
•	а	mADAM-TS1 hADAM-TS2 hADAM-TS3 hADAM-TS4 mADAM-TS5 hADAM-TS6 hADAM-TS7	HELGHVFNMP HD HETGHVLGME HD HETGHVLGME HD HELGHVFNML HD HEIGHL LG LS HD HEIVHN FGMN HD HELGH S FG I Q HD	
	mADAM-TS1 hADAM-TS2 hADAM-TS3 hADAM-TS4 hADAM-TS5 hADAM-TS6 hADAM-TS6	W G P W G P W G A W S P W G A W S P W G S W G S W G S W G S W G S A W S A	FGSCSRTCGTGVKFFEGSCSRTCGGGVQFFWGGCSRTGCGGGVQFF	20 ·· . 20 20 20 20 20 20
b	mADAM-TSI hADAM-TS2 hADAM-TS3 hADAM-TS4 hADAM-TS5 hADAMI-TS6 hADAM-TS7	T M R E C D R T R Q C D R T R Q C D S S R D C C T A Y R H C D A E R Q C T	N P H P A N G G R T C S G L R P Y P R N G G K Y C E G R R P A P R N N G G K Y C L G E	40 40 40 40 40 40 40
	mADAM-TS1 hADAM-TS2 hADAM-TS3 hADAM-TS4 hADAM-TS5 hADAM-TS6 hADAM-TS7	R V R Y R S A Y D F Q L A Y D F O L R T R F R S R A I Y H S R K R F R L	C NS QD C C NT E D C C NT D P C	52 52 52 52 52 52 52 52

Fig. 13 (con't)





THROMBOSPONDIŅ TYPE I REPEAT CYSTEINE-POOR DOMAIN CYSTEINE-RICH DOMAIN ADAM-TS RELATED PROTEIN-1 (ADAM-TSR1) UNIQUE DOMAINS ADAM-TSR1 525 a.a. Fig. 15 DISINTEGRIN-LIKE DOMAIN METALLOPROTEASE DOMAIN SIGNAL PEPTIDE PRO-DOMAIN ADAM-TS1 951 a.a. ż

SUBSTITUTE SHEET (RULE 26)

#### FIGURE 16

MSSCFVWPAMRSPSPPAWTTTGHCWPSRHLLP 40 GAAPRHGGHSRVPPLLQSGLASTHFLLNLTRSSRLLAGRV 80 SVEYWIREGLAWQRAARPHCLYAGHLQGQASSSHVAISTC 120 GGLHGLIVADEEEYLIEPLHGGPKGSRSPEESGPHVVYKR 160 SSLRHPHLDTACGVRDEKPWKGRPWWLRTLKPPPARPLON 200 ETERGOPGLKRSVSRERYVETLVVADKMMVAYHGRRDVEQ 240 YVLAIMNIVAKLFQDSSLGSTVNILVIRLILLIEDQPILE 280 ITHHAGKSLDSFCKWQKSIVNHSGHGVAIPENGVANHDIA 320 VLITRYDICTYKNKPCGTLGLARWAECVSAREAAASMRTL 360 AATSVHHCHEIGHIFGMNHDGVGNSCGARGQDPAKLMAAH 400 ITMKINPFVWSSCNRDYITSFLDSGLGLCLNNRPPRQDFV 440 YPTVAPGQAYDADEQCRFQHGVKSRQCKYGEVCSELWCLS 480 KSNRCIINSIPAAEGILCQIHTIDKGWCYKRVCVPFGSRP 520 EGVDGAWGPWTFWGDCSRTCGGGVSSSSRHCDSPRPTTGG 560 KYCLGERRRHRSCNIDDCPPGSQDFREVQCSEFDSIPFRG 600 KFYKWKTYRGGGVKACSLTSLAEGFNFYTERAAAVVDGIP 640 CRPDIVDICVSGECKHVGCDRVLGSDLREDKCRVCGGDGS 680 ACETIEGVFSPASPGAGYEDVVWIPKGSVHIFIQDLNLSL 720 SHLALKGDQESLLLEGLPGTPQPHRLPLAGTTFQLRQGPD 760 QVQSLEALGPINASLIVMVLARTELPALRYRFNAPIARDS 800 LPPYSWHYAPWIKCSAQCAGGSQVQAVECRNQLDSSAVAP 840 HYCSAHSKLPKRORACNTEPCPPDWVVGWSLCSRSCDAG 880 VRSRSVVCQRRVSAAEEKALDDSACPQPRPPVLEACHGPT 920 CPPEWAALDWSECTPSCGPGLRHRVVLCKSADHRATLPPA 960 HCSPAAKPPATMRCNLRRCPPARWVAGEWGECSAQCGVGO 1000 RQRSVRCTSHTGQASHECTEALRPPTTQQCEAKCDSPTPG 1040 DGPEECKDVNKVAYCPLVLKFQFCSRAYFRQMCCKTCQGH 1080 Created: Thursday, October 01, 1998 11:05 PM

	10	20	30	40	
سلست	لستنكيب	سيسلسينا	سيلسيا	لبيبيا	
tcacgca	acgccttc	ggtctcaag	ATGAGITCC	TGTCCAG	40
TCTGGAC	AGCTATG!	AGATCGCCTT	CCCACCCG	CGTGGAC	80
CACAACC	EGGCACT(	CTGGCCTTC	TOGOCACCT	CTCCCC	120
GGAGCAC	3CGCCCGCG	GCALCGGGGGG	CACAGOOGA	TCCCCC	160
CICTIC	DACAAAGIO	GCCTCGCCA(	CACCCACT	ICCIGCT	200

210 220 230 240	
<u> </u>	
GAACCTGACCCGCAGCTCCCGTCTACTGGCAGGCCGCGTC 240	
TCCGTGGAGTACTGGACACGGGAGGGCCTGGCCTGGCAGA 280	
GGGCGGCCCGCCCCCCCCCCCCCCCCCCCCCCCCCCCC	
GGGCCAGGCCAGCICCCATGIGGCCATCAGCACCIGI 360	
GCAGGCCTGCACGCCTGATCGTGGCAGACGAGGAAGAGT 400	
410 420 430 440	
milion in the second se	
ACCTGATTGAGCCCCTGCACGGTGGGCCCCAAGGGTTCTCG 440	
GAGCCCGCAGGAAAGTGGACCACATGTGGTGTACAAGCGT 480	
TCCTCTCTGCGTCACCCCCACCTGGACACAGCCTGTGGAG 520	
TCAGAGATGAGAAACCGTCGAAAGGCCGGCCATGGTGGCT 560	
GCCGACCTTGAAGCCACCCCCTGCCAGACCCCTGGGGAAT 600	
610 620 630 640	
and military and a second seco	
GAAACAGAGCGTGGCCAGCCAGGCCTGAAGCGATCGGTCA 640	
GCCGAGAGCGCTACGTGGAGACCCTGGTGGTGGCTGACAA 680	
CATGATGGTGGCCTATCACGGGCGCGCGCATGTGGAGCAG 720	
TATGTCCTGGCCATCATGAACATTGTTGCCCAAACTTTTCC 760	
AGGACTOGAGTCTGGGAAGCACCGTTAACATCCTCGTAAC 800	
810 820 830 840	
andmilantmilantmilantmil	
TOGOCTCATOCTGCTCACGGAGGACCAGCCCACTCTGGAG 840	
ATCACCCACCATGCCGGGAAGTCCCTAGACAGCTTCTGTA 880	
AGTGGCAGAAATCCATCGTGAACCACAGCGGCCATGGCAA 920	
TGCCATTCCAGAGAACGGTGTGGCTAACCATGACACAGCA 960	
GIGCICATCACACGCIATGACATCIGCATCITACAAGAACA 1000	
1010 1020 1030 1040	
and and make the control of the cont	
AACCCTGCGGCACACTAGGCCTGGCCCGGTGGGCGGAATG 1040	
TGTGAGCGCGAGAGAGCTGCAGCGTCAATGAGGACATTG 1080	
GCTGCCACAAGCGTTCACCATTGCCACGACATCGGGCACA 1120	
CATTCGCCATGAACCATGACGCGIGGCAAACAGCTGTGG 1160	
GCCCGTGGTCAGGACCCAGCCAAGCTCATGGCTGCCCAC 1200	

1210 1220 1230 1240
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ACCGTGACTACATCACCAGCTTTCTAGACTCGGGCCTGGG 1280
GCTCTGCCTGAACAACCGGCCCCCAGACAGGACTTTGTG 1320
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1410 1420 1430 1440
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GAGGGTGTGGACGCACCCTGGGGGCCCGTGGACTCCATGGG 1600
1610 1620 1630 1640
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GCAAGCACGTGGGCTGCGACCGAGTCCTGGGCTCCGACCT 2000
2010 2020 2030 2040
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CICCGICCACATCITCATCCAGGATCTGAACCTCTCTCTC 2160
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2210 2220 2230 2240	
and make the state of the state	
TGGAGGGGTGCCTGGGACCCCCAGCCCCACCGTCTGCC 2240	
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CGAGICGGGIGAGIGCICIGCACAGIGCGCGGCGICGGGCAG 3000	
3010 3020 3030 3040	
and make the control of the control	-
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3210 3220 3230 3240
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cggggggggggaactgggaagggtgagacggagcc 3360
ggaagttatttattgggaacccctgcagggccctggctgg
3410 3420 3430 3440
ggggatoga 3409

#### FIGURE 17

Molecular Weight 216301.30 Daltons 1934 Amino Acids 234 Strongly Basic(+) Amino Acids (K,R) 216 Strongly Acidic(-) Amino Acids (D,E) 477 Hydrophobic Amino Acids (A,I,L,F,W,V) 657 Polar Amino Acids (N,C,Q,S,T,Y)

7.734 Isolectric Point 24.102 Charge at PH 7.0

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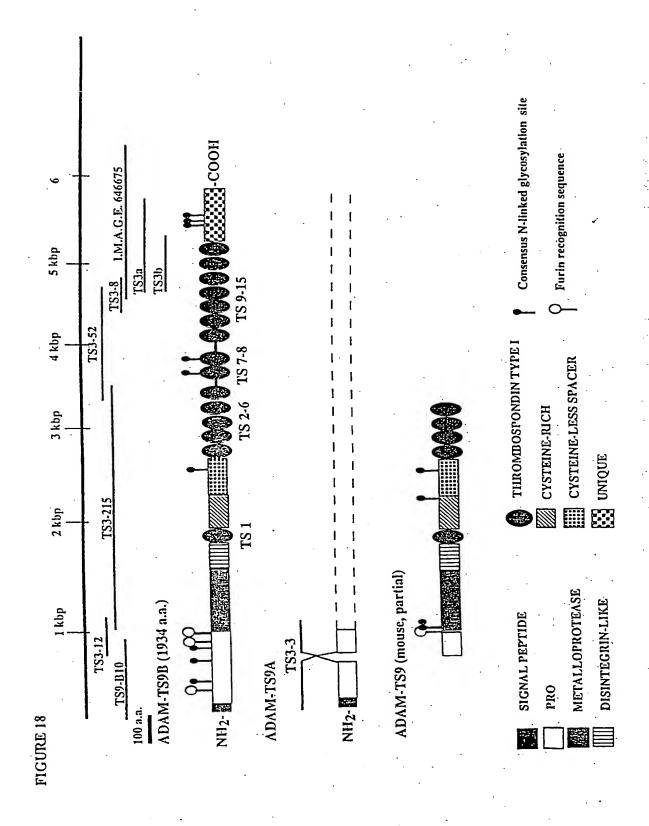
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15	tca		acg						atg Met								48
20									gcg Ala 25								96
25									gga Gly								144
23									caa Gln								192
30									tcc Ser								240
35									ggc Gly								288
40									cac His 105								336
45				_		_		_	gga Gly		_			_			384
43									gag Glu								432
50									gga Gly								480
55									gac Asp								528
60			_						tgg Trp 185		_			_	_		576
	Pro			Arg					gaa Glu								624
65		aag	cga	tcg	gtc	agc	cga	gag	cgc	tac	gtg	gag	acc	atg	gat	gtg	672

	Leu	Lys 210	Arg	Ser	Val	Ser	Arg 215	Glu	Arg	Tyr	Val	Glu 220	Thr	Met	Asp	Val	
5	gct Ala 225	gac Asp	aag Lys	atg Met	atg Met	gtg Val 230	gcc Ala	tat Tyr	cac His	G1y 999	cgc Arg 235	cgg Arg	gat Asp	gtg Val	gag Glu	cag Gln 240	720
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	Gln	Val	Gln 755	Ser	Leu	Glu	Ala	Leu 760	Gly	Pro	Ile		Ala 765	Ser	Leu	Ile
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	His	Tyr	Cys 835	Ser	Ala	His	Ser	Lys 840	Leu	Pro	Lys	Arg	Gln 845	Arg	Ala	Cys
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					885					890					Ser 895	
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					965					970				•	Arg 975	_
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1045

1050

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10			aca Thr														725
			aaa Lys														773
15	att Ile	aac Asn	ctg Leu 250	gct Ala	ggt Gly	gac Asp	gta Val	gca Ala 255	gca Ala	tta Leu	aac Asn	agc Ser	ggc Gly 260	tta Leu	gca Ala	aca Thr	821
20			ttt Phe														869
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35			gac Asp 330														1061
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20	Ala 145	Glu	Leu	Lys	His	Cys 150	Phe	Tyr	Lys	Gly	Tyr 155	Val	Asn	Thr	Asn	Ser 160
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35	Thr 225	Ser	Glu	His	Lys	Asn 230	Arg	His	Ser	Lys	Asp 235	Lys	Lys	Lys	Thr	Arg 240
	Ala	Arg	Lys	Trp	Gly 245	Glu	Arg	Ile	Asn	Leu 250	Ala	Gly	Asp	Val	Ala 255	Ala
40	Leu	Asn	Ser	Gly 260	Leu	Ala	Thr	Glu	Ala 265	Phe	Ser	Ala	Tyr	Gly 270	Asn	Lys
	Thr	Asp	Asn 275	Thr	Arg	Glu	Lys	Arg 280		His	Arg	Arg	Thr 285	Lys	Arg	Phe
45	Leu	Ser 290	Tyr	Pro	Arg	Phe	Val 295	Glu	Val	Leu	Val	Val 300	Ala	Asp	Asn	Arg
50	Met 305	Val	Ser	Tyr	His	Gly 310	Glu	Asn	Leu	Gln	His 315	Tyr	Ile	Leu	Thr	Leu 320
	Met	Ser	Ile	Val	Ala 325	Ser	Ile	Tyr	Lys	Asp 330	Pro	Ser	Ile	Gly	Asn 335	Leu
55	Ile	Asn	Ile	Val 340	Ile	Val	Asn	Leu	11e 345	Val	Ile	His	Asn	Glu 350	Gln	Asp
	Gly	Pro	Ser 355	Ile	Ser	Phe	naA	Ala 360	Gln	Thr	Thr	Leu	Lys 365	Asn	Phe	Cys
60	Gln	Trp 370	Gln	His	Ser	Asn	Ser 375	Pro	Gly	Gly	Ile	His 380	His	Asp	Thr	Äla
65	Val 385	Leu	Leu	Thr	Arg	Gln 390	Asp	Ile	Cys	Arg	Ala 395	His	Asp	Lys	Cys	Asp 400
	Thr	Leu	Gly	Leu	Ala	Glu	Leu	Gly	Thr	Ile	Cys	Asp	Pro	Tyr	Arg	Ser

					405					410					415	
5	Cys	Ser	Ile	Ser 420	Glu	Asp	Ser	Gly	Leu 425	Ser	Thr	Ala	Phe	Thr 430	Ile	Ala
J	His	Glu	Leu 435	Gly	His	Val	Phe	Asn 440	Met	Pro	His	Asp	Asp 445	Asn	Asn	Lys
10	Cys	Lys 450	Glu	Glu	Gly	Val	Lys 455	Ser	Pro	Gln		Val 460	Met	Ala	Pro	Thr
	Leu 465	Asn	Phe	Tyr	Thr	Asn 470	Pro	Trp	Met	Trp	Ser 475	Lys	Cys	Ser	Arg	Lys 480
15	Tyr	Ile	Thr	Glu	Phe 485	Leu	Asp	Thr	Gly	Tyr 490	Gly	Glu	Cys	Leu	Leu 495	Asn
20	Glu	Pro	Glu	Ser 500	Arg	Pro	Tyr	Pro	Leu 505	Pro	Val	Gln	Leu	Pro 510	Gly	Ile
20	Leu	Tyr	Asn 515	Val	Asn	Lys	Gln	Cys 520	Glu	Leu	Ile	Phe	Gly 525	Pro	Gly _/	Ser
25	Gln	Val 530	Cys	Pro	Tyr	Met	Met 535	Gln	Cys	Arg	Arg	Leu 540	Trp	Ser	Asn	Asn
	Val 545	Asn	Gly	Val	His	Lys 550	Gly	Сув	Arg	Thr	Gln 555	His	Thr	Pro	Trp	Ala 560
30	Asp	Gly	Thr	Glu	Сув 565	Glu	Pro	Gly	Lys	His 570	Сув	Lys	Tyr	Gly	Phe 575	Cys
35	Val	Pro	Lys	Glu 580	Met	Asp	Val	Pro	Val 585	Thr	Asp	Gly	Ser	Trp 590	Gly	Ser
,,,	Trp	Ser	Pro 595	Phe	Gly	Thr	Cys	Ser 600	Arg	Thr	Cys	Gly	Gly 605	Gly	Ile	Lys
40	Thr	Ala 610	Ile	Arg	Glu	Cys	Asn 615	Arg	Pro	Glu	Pro	Lys 620	Asn	Gly	Gly	Lys
	Tyr 625	Cys	Val	Gly	Arg	Arg 630	Met	Lys	Phe	Lys	Ser 635	Cys	Asn	Thr	Glu	Pro 640
45	Cys	Leu	Lув	Gln	Lys 645	Arg	Asp	Phe	Arg	Asp 650	Glu	Gln	Сув	Ala	His 655	Phe
50	Asp	Gly	Lys	His 660	Phe	Asn	Ile	Asn	Gly 665	Leu	Leu	Pro	Asn	Val 670	Arg	Trp
	Val	Pro	Lys 675	Туг	Ser	Gly	Ile	Leu 680	Met	Lys	Asp	Arg	Cys 685	Lys	Leu	Phe
55	Cys	Arg 690	Val	Ala	Gly	Asn	Thr 695	Ala	Tyr	Tyr	Gln	Leu 700	Arg	Asp	Arg	Val
	Ile 705	Asp	Gly	Thr	Pro	Сув 710	Gly	Gln	Asp	Thr	Asn 715	Asp	Ile	Суз	Val	Gln 720
60	Gly	Leu	Cys	Arg	Gln 725	Ala	Gly	Сув		His 730	Val	Leu	Asn	Ser	Lys 735	Ala
65	Arg	Arg	Asp	Lys 740	Cys	Gly	Val	Cys	Gly 745	Gly	Asp	Asn	Ser	Ser 750	Сув	Lys
Ų J	Thr	Val	Ala	Gly	Thr	Phe	Asn	Thr	Val	His	Tyr	Gly	Tyr	Asn	Thr	Val

			755					760					765			
5	Val	Arg 770	Ile	Pro	Ala	Gly	Ala 775	Thr	Asn	Ile	Asp	Val 780	Arg	Gln	His	Ser
_	Phe 785	Ser	Gly	Glu	Thr	Asp 790	Asp	Asp	Asn	Tyr	Leu 795	Ala	Leu	Ser	Ser	Ser 800
10	Lys	Gly	Glu	Phe	Leu 805	Leu	Asn	Gly	Asn	Phe 810	Val	Val	Thr	Met	Ala 815	Lys
,	Arg	Glu	Ile	Arg 820	Ile	GĴĄ	Asn	Ala	Val 825	Val	Glu	Tyr	Ser	Gly 830	Ser	Glu
15	Thr	Ala	Val 835	Glu	Arg	Ile	Asn	Ser 840	Thr	Asp	Arg	Ile	Glu 845	Gln	Glu	Leu
20	Leu	Leu 850	Gln	Val	Leu	Ser	Val 855	Gly	Lys	Leu	Tyr	Asn 860	Pro	Asp	Val	Arg
20	Tyr 865	Ser	Phe	Asn	Ile	Pro 870	Ile	Glu	Asp	Lys	Pro 875	Gln	Gln	Phe	Tyr	Trp 880
25	Asn	Ser	His	Gly	Pro 885	Trp	Gln	Ala	Ċys	Ser 890	Lys	Pro	Сув	Gln	Gly 895	Glu
	Arg	Lys	Arg	Lys 900	Leu	Val	Сув	Thr	Arg 905	Glu	Ser	Asp	Gln	Leu 910	Thr	Val
30	Ser	Asp	Gln 915	Arg	Cys	Asp	Arg	Leu 920	Pro	Gln	Pro	Gly	His 925	Ile	Thr	Glu
35	Pro	Cys 930	Gly	Thr	Gly	Сув	Asp 935	Leu	Arg	Trp	His	Val 940	Ala	Ser	Arg	Ser
,,	Glu 945	Cys	Ser	Ala	Gln	Cys 950	Gly	Leu	Gly	туг	Arg 955	Thr	Leu	Asp	Ile	Tyr 960
40	Cys	Ala	Lys	Tyr	Ser 965	Arg	Leu	Asp	Gly	Lys 970	Thr	Glu	Lys	Val	Asp 975	Asp
	Gly	Phe	Cys	Ser 980	Ser	His	Pro	Lys	Pro 985	Ser	Asn	Arg	Glu	Lys 990	Cys	Ser
45	Gly	Glu	Сув 995		Thr				Arg		Ser		Trp 1005		Glu	Cys
50		Lys 1010	Ser	Cys	Asp		Gly 1015	Thr	Gln	Arg		Arg 1020	Ala	Ile	Суѕ	Val
50	Asn 1025		Arg	Asn	Asp	Val 1030	Leu	Asp	Asp		Lys 1035	Сув	Thr	His		Glu L040
55	Lys	Val	Thr		Gln 1045	Arg	Cys	Ser		Phe 1050	Pro	Cys	Pro		Trp 1055	Lys
	Ser	Gly		Trp 1060	Ser	Glu	Cys		Val 1065	Thr	Сув	Gly		Gly 1070	His	Lys
60	His		Gln 1075	Val	Trp	Cys		Phe L080	Gly	Glu	Asp	_	Leu 1085	Asn	Asp	Arg
65		Cys 1090	Asp	Pro	Glu		Lys 1095	Pro	Thr	Ser		Gln 1100	Thr	Cys	Gln	Gln
	Pro	Glu	Met	Ala	Ser	Trp	Gln	Ala	Gly	Pro	Trp	Val	Gln	Сув	Ser	Val

	110	•				1110					1115					1120
5	Thr	Cys	Gly		Gly 1125		Gln	Leu		Ala 1130		Lys	Cys		Ile 1135	
J	Thr	Tyr		Ser 1140	Val	Val	Asp		Asn 1145	Asp	Cys	Asn		Ala 1150	Thr	Arg
10	Pro		Asp L155	Thr	Gln	Asp		Glu 1160	Leu	Pro	Ser		His 1165	Pro	Pro	Pro
		Ala 170	Pro	.Glu	Thr		Arg 1175	Ser	Thr	Tyr		Ala 1180	Pro	Arg	Thr	Gln
15	Trp 1185	Arg	Phe	Gly		Trp 1190	Thr	Pro	Cys		Ala 1195	Thr	Cys	Gly	_	Gly 1200
20				:	Tyr 1205					1210				:	1215	
				1220	Cys				1225				:	1230		
25		1	235		Pro		1	1240					1245			
	1	250			Cys	:	1255					1260				
30	Val 1265				3	1270		•			1275				1	L280
35				1	Thr 1285				3	1290		•		1	1295	
			1	L300	Ser			3	L305				1	L310		
40		1	315		Ser		1	.320				1	1325		_	_
45		330				J	L335			-	1	1340			_	
45	Gly 1345				1	1350				1	1355				1	360
50				1	Cys 1365				1	1370				נ	375	
	Cys		1	1380			•	1	385				1	390		
55	Cys	1	395				1	400				1	405			-
60		410				1	.415				1	420				
	Asp 1425				1	430				1	435			•	1	440
65	Asp			. 1	445				1	450				1	455	-
	- 4		4		-,-					- 1 -	-10			442	$\alpha \circ \cup$	31 V

			1	460				1	465				1	.470		
5	Ser		Leu .475	Glu	Ser	qsA		Cys 480	Lys	His	Leu	Ala 1	Lys 485	Pro	His	Gly
3		Arg 490	Lys	Сув	Arg		Gly 1495	Arg	Cys	Pro		Trp 1500	Lys	Ala	Gly	Ala
10	Trp 1505		Gln	Cys		Val 1510	Ser	Cys	Gly		Gly 515	Val	Gln	Gln		His .520
	Val	Gly	Cys		11e 525	Gly	Thr	His		11e .530	Ala	Arg	Asp		Glu .535	Cys
15	Asn	Pro		Thr 540	Arg	Pro	Glu		Glu 1545	Суѕ	Glu	Cys		Gly .550	Pro	Arg
20	Cys		Leu .555	Tyr	Thr	Trp		Ala 560	Glu	Glu	Ser	Gln 1	Glu .565	Cys	Thr	Lys
_ •		Cys .570	Gly	Glu	Gly		Arg L575	Tyr	Arg	Lys		Val 1580	Cys	Val	qeA	Asp
25	Asn 1585	-	Asn	Glu		His 1590	Gly	Ala	Arg		Asp 1595	Val	Ser	Lys		Pro 1600
	Val	Asp	Arg		Ser L605	Сув	Ser	Leu		Pro 1610	Cys	Glu	Tyr		Trp .615	Ile
30	Thr	Gly		Trp L620	Ser	Glu	Cys		Val 1625	Thr	Cys	Gly		Gly 1630	Tyr	Lys
35	Gln	_	Leu 1635	Val	Ser	Cys		Glu L640	Ile	Tyr	Thr	Gly	Lys .645	Glu	Asn	Tyr
		Tyr 1650	Ser	Tyr	Gln		Thr 1655	Ile	Asn	Cys		Gly 1660	Thr	Gln	Pro	Pro
40	Ser 1669		His	Pro		Tyr 1670	Leu	Arg	Glu		Pro L675	Val	Ser	Ala		Trp 1680
	Arg	Val	Gly		Trp 1685	Gly	Ser	Cys		Val 1690	Ser	Cys	Gly		Gly 1695	Val
45	Met	Gln		Ser 1700	Val	Gln	Суѕ		Thr 1705	Asn	Glu	Asp		Pro 1710	Ser	His
50	Leu	-	His 1715	Thr	Asp	Leu		Pro 1720	Glu	Glu	Arg	Lys	Thr 1725	Cys	Arg	Asn
		Tyr 1730	Asn	Cys	Glu		Pro 1735	Gln	Asn	Сув		Glu 1740	Val	Lys	Arg	Leu
55	Lys 174		Ala	Ser		Asp 1750	Gly	Glu	Tyr		Leu 1755	Met	Ile	Arg		Lys 1760
	Leu	Leu	Lys		Phe 1765	Сув	Ala	Gly		His 1770	Ser	Asp	His		<b>Lys</b> 1775	Glu
60	Tyr	Val		Leu 1780	Val	His	Gly		Ser 1785	Glu	Asn	Phe		Glu 1790	Val	Tyr
	Gly	His	Arg	Leu	His	Asn	Pro	Thr	Glu	Сув	Pro	Tyr	Asn	Gly	Ser	Arg

Arg Asp Asp Cys Gln Cys Arg Lys Asp Tyr Thr Ala Ala Gly Phe Ser

1810 1815 1820

Ser Phe Gln Lys Ile Arg Ile Asp Leu Thr Ser Met Gln Ile Ile Thr 1825 1830 1835 1840

Thr Asp Leu Gln Phe Ala Arg Thr Ser Glu Gly His Pro Val Pro Phe 1845 1850 1855

Ala Thr Ala Gly Asp Cys Tyr Ser Ala Ala Lys Cys Pro Gln Gly Arg 10 1860 1865 1870

Phe Ser Ile Asn Leu Tyr Gly Thr Gly Leu Ser Leu Thr Glu Ser Ala 1875 1880 1885

15 Arg Trp Ile Ser Gln Gly Asn Tyr Ala Val Ser Asp Ile Lys Lys Ser 1890 1895 1900

Pro Asp Gly Thr Arg Val Val Gly Lys Cys Gly Gly Tyr Cys Gly Lys 1905 1910 1915 1920

Cys Thr Pro Ser Ser Gly Thr Gly Leu Glu Val Arg Val Leu 1925 1930

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